CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-337/S018	
Brand Name:	INVANZ™
Generic Name:	Ertapenem Sodium
Dosage Form:	Injection: Intravenous/Intramuscular
Dosage Strength:	1 GM
Indication:	Treatment of moderate to severe infections.
NDA Type:	Efficacy Supplement Pediatric Written Request
Relevant NDA/IND	NDA 21-337/IND 48,485
Submission Date(s):	11/19/04
Sponsor:	Merck & Co. Inc., Rahway, NJ
Reviewer:	Chandra S. Chaurasia, Ph.D.
Team Leader:	Venkateswar Jarugula, Ph. D
OCPB Division:	DPE III (HFD-880)
OND Division:	DAIDP (HFD-520)

1. EXECUTIVE SUMMARY

Ertapenem (INVANZ™/ MK-0826) is a long-acting parenteral 1-β-methyl carbapenem antibiotic and is indicated for the treatment of various community acquired and mixed infections in adults.

The Sponsor has submitted this supplemental NDA in response to Pediatric Written Request dated May 04, 2004. The studies in the pediatric program were all performed in response to and in accordance with the PWR and its amendments.

The pivotal PK study protocol #28 was conducted to investigate the pharmacokinetics, safety, and tolerability of ertapenem in patients aged 3 months- to 17 years, and to determine a therapeutic dose of ertapenem for this population. The study enrolled 84 male and female patients distributed among the following age strata: 3 months to 23 months (N=43), 2 to 12 years (N=28), and 13 to 17 years (N=13). A single 20- and 40-mg/kg IV doses of ertapenem were administered to these patients. The parameters AUC(0-∞), Ceoi (concentrations at

end of infusion), C12hr (concentration at the midpoint of the dosing interval), and plasma clearance (CLp) were used in comparing the PK profiles between the pediatric and adult populations (data from historic control).

Based on the results of 20 mg/kg and 40 mg/kg dosing, protocol#28 was amended to include 15 mg/kg single dose IV in order to determine a therapeutic dose of ertapenem for patients 3 months- to 12 years of age. The C6hr (concentration at the midpoint) was used to assess the potential for twice daily dosing in children 3-months to 12-years of age for the 15 mg/kg dose.

A summary of the pediatric clinical pharmacology study results are provided below:

The plasma clearance of ertapenem, on a per kg body weight basis following 15-mg/kg, 20-mg/kg, or 40-mg/kg doses in children 3 to 23 months and 2 to 12 years of age were approximately 2-fold higher compared to those in adults following a 1 g dose.

The volume of distribution at steady state (0.2 liter/kg) in pediatric patients 3 months to 12 years of age following 20-mg and 40-mg/kg doses was 67% higher than that in the adults (0.12 liter/kg) following 1 g dose.

The mean AUC(0-∞) values following 20-mg/kg dose for the 3-23 months and 2-12 years cohorts were about 65% of the adult AUC(0-∞), whereas, those for the 40-mg/kg dose in the pediatric cohorts were similar to adults.

Consistent with other β-lactam antibiotics, the PK/PD parameter for predicting efficacy of ertapenem is associated with the time the plasma concentration remained above MIC (%T>MIC). The plasma concentrations of ertapenem at the midpoint of the dosing interval for once-daily dosing, C12hr, provides as a guide to predict efficacy in the treatment of aerobic pathogens. The mean C12 hr values in children 3 to 23 months and 2 to 12 years of age following 20 mg/kg (2.6-3.3 µg/mL) and 40 mg/kg (5.9-6.6 µg/mL) once daily dosing, were lower than that in healthy adults (8.9 µg/mL). Although the mean C12 hr values were above the susceptibility breakpoint of 2 µg/mL, 2 out of 12 children in the age group of 3 to 23 months and 2 out of 9 children in the age group of 2 to 12 years at 20 mg/kg dose; and 1 out of 13 in the 3 to 23 months age group at 40 mg/kg dose had C12 hr values below 2 µg/mL.

Considering the higher clearance of ertapenem in pediatric 3 months to 12 years of age, if given as a single daily dose, the plasma ertapenem concentrations at 12hr for these patients might be below the desired plasma target of 2 µg/mL. In order to achieve higher plasma concentrations at the midpoint of dosing interval without considerably increasing either the Ceoi or AUC (which might increase potential for adverse reactions), a 15 mg/kg twice daily dosing regimen for children 3 to 23 moths and 2 to 12 years was studied. The C6 hr (the midpoint of the intended twice-daily dosing interval) values for total ertapenem following the administration of single 15-mg/kg IV doses to patients 3 to 23 months and 2 to 12 years of age were slightly higher (12.7 and 10.7 µg/mL, respectively) than the C12h concentration in healthy young adults (8.9 µg/mL), and well above the breakpoint of 2 µg/mL.

With respect to the adolescent patients (13 to 17 years), the mean plasma clearance on a per kg basis following the 20-mg/kg (0.60 mL/min/kg) and 40 mg/kg (0.63 mL/min/kg) dose were only slightly higher than that following a 1g dose to healthy young adults (0.43 mL/min/kg). In addition, the AUC, Ceoi and C12 values were similar to those observed in the adult population following 1 g dosing. Thus, the 1 g once daily dose similar to that in the adult population was proposed for this population.

The 15 mg/kg twice daily dose in 3 months to 12 years of age and 1 g once daily dose in 13-17 years of age was shown to be safe and effective in the two Phase 3 clinical trials.

Regarding the Written Request for therapeutic usage of ertapenem in pediatric patients with meningitis, Study (Protocol 031/32) was conducted to evaluate the cerebrospinal fluid concentrations of ertapenem after intravenous administration in these pediatric population. The results of the study showed insufficient CSF concentrations to cover all relevant pathogens, and in the Final Amended PWR 04 May, 2004 the FDA concurred with the removal of the pediatric meningitis efficacy study as a requirement for the ertapenem pediatric program.

1.1. Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the supplement NDA 21-337. The information submitted are acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. Based on lack of evidence of sufficient penetration of ertapenem into the CSF, the labeling should be amended to incorporate that INVANZ is NOT INDICATED in the treatment of meningitis in the pediatric population.

The proposed labeling recommendations in Section 3 should be communicated to the Sponsor as appropriate.

1.2. Phase IV Commitments: None requested from Clinical Pharmacology and Biopharmaceutics perspectives.

Chandra S. Chaurasia, Ph.D._____ Date: _____
Clinical Pharmacology and Biopharm Reviewer
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RD/FT Initialed by Venkateswar Jarugula, Ph.D. _____Date: _____
Team Leader
Division of Pharmaceutical Evaluation III

CC: Division File NDA 21-337, HFD-520 (CSO/S. Samanta), HFD-520 (MO/ T. Smith, L. Forsyth), (HFD-880 (J. Lazor, A. Selen, V. Jarugula, C. Chaurasia)

2. Question-Based Review

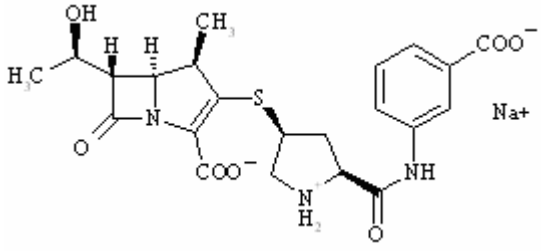
2.1. General Attributes

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and Biopharmaceutics of the drug?

Invanz (Etrapenem Sodium) was approved on Nov 21, 2001 for the treatment of adults with severe to moderate infections caused by susceptible strains of designated microorganism. Pursuant to CFR 21, Section 505(b) and the "Best Pharmaceuticals for Children Act", and in response to the Agency's May 15, 2000 Written Request, along with its April 12, 2002 and May 4, 2004 amendments, the Sponsor has submitted this supplemental New Drug Application to NDA 21-337, Invanz for the Agency's review, and approval.

What is the chemical structure and formulation of Ertapenem**?**

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.

What is the therapeutic indication?

INVANZ is indicated for the treatment of patients with moderate to severe infections caused by susceptible strains of the designated microorganisms.

What are the proposed dosage and route of administration?

Sponsor's proposed dosing recommendation in pediatric population as follows:

The dose of INVANZ in patients 13 years of age and older is 1 gram (g) given once a day. The proposed 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.

In the original NDA 21-337, the reported absolute bioavailability for ertapenem IM 1 g dose was 90% compared to the 1 g IV dose with a 90% confidence interval of 0.87 to 0.93. It is also noted that in the adult population the average plasma ertapenem concentrations at 6 and 12 hrs following IM administration were 40 and 13 µg/mL, respectively vs. 31 and 9 µg/mL following IV dosing (Table 1 in the approved Invanz package insert). Furthermore, the mean C6hr values (midpoint of bid dosing) in pediatric patients 3 months to 12 years of age (10.7 and 12.7 µg/mL, respectively) are not only greater than that of the mean C12hr value of 8.9 µg/mL in adults, but also well above the critical susceptibility breakpoint concentration of 2 µg/mL. Thus, although no PK study on IM administration in pediatric population has been conducted, any potential variability in plasma concentrations following IM administration is unlikely to affect the efficacy of ertapenem —in terms of critical breakpoint concentration of 2 µg/mL. Additionally, in the clinical trial in pediatric population, 3 months to 17 years, IM therapy was given to 7 patients, and was well tolerated (primary endpoint).

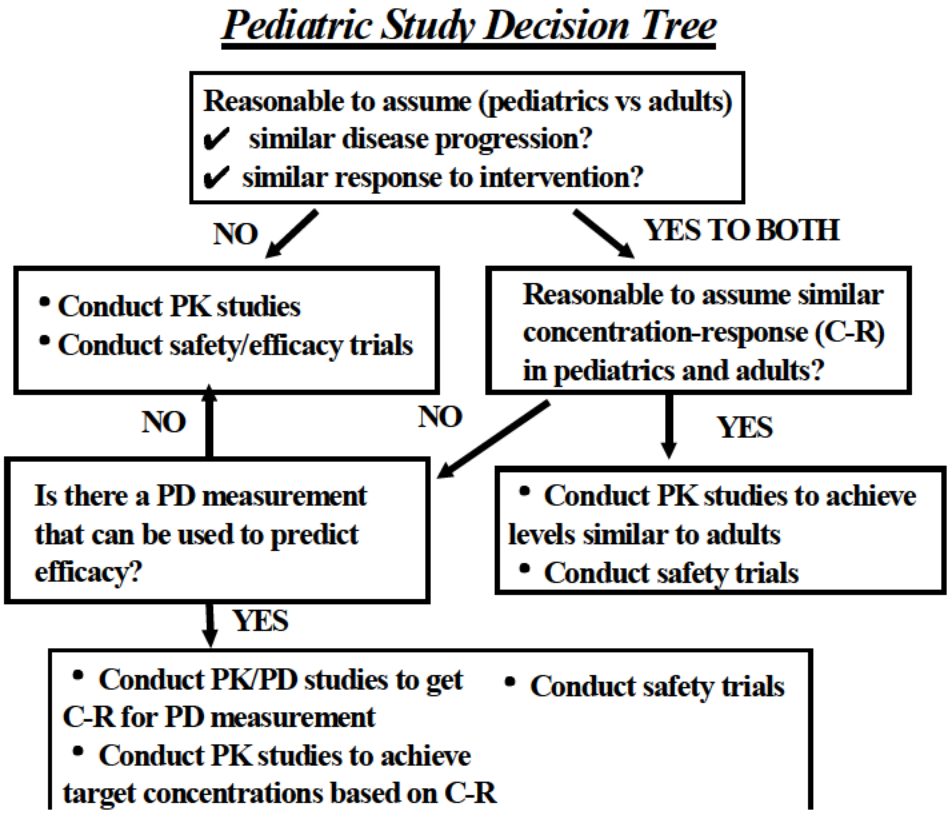
2.2. Pediatric Study Decision Tree

Is it reasonable to assume similar disease progression in pediatrics vs. adults?

YES. Similar to other drugs in the class, ertapenem blocks bacterial cell-wall synthesis by binding to specific penicillin binding proteins (PBPs). Because the pathophysiologic processes and bacterial pathogens in the infectious diseases currently licensed for ertapenem use are generally similar for children and adults, when caused by susceptible bacteria, these infections in children as in adults respond effectively to β-lactam antibiotics.

Is it reasonable to assume a similar response to treatment in pediatrics vs. adults?

YES. The present application for ertapenem covers age groups in which pediatric usage of ertapenem for the currently approved indications is anticipated to occur should pediatric licensure be granted. Three of the six infectious disease indications currently licensed in adults for ertapenem (serious community-acquired pneumonia, urinary tract infections and skin infections) are frequently encountered in children between the ages of 3 months to 17 years of age. Intra-abdominal infections in children most commonly arise as a complication of acute appendicitis and therefore occur generally in children above 2 years of age. Based on the similarity of the pathophysiologic reasons given above, efficacy in adults in these indications may reliably be extrapolated to children. Therefore, the Sponsor followed right-side path of the Pediatric Study Decision Tree, and conducted two Phase 3 clinical trials in pediatric patients.



2.3. General Clinical Pharmacology

2.3.1. Intrinsic Factors

2.3.1.1. Does age influence the pharmacokinetics and PK/PD of ertapenem in pediatric patients?
Plasma Clearance (CLp):
As shown in Table 1 below, age affects plasma clearance between the pediatric and adult population. The plasma clearance on a per kg basis following 15-mg/kg (geometric mean 0.94 mL/min/kg ±20, range 0.60-1.31, N=12) or 20-mg/kg (geometric mean 0.99 mL/min/kg, 0.32, range 0.36-1.38, N=8) doses in children 3 to 23 months and 2 to 12 years of age were approximately 2-fold higher, as compared to that of 0.43 mL/min/kg in healthy adults following the administration of a 1 g dose. Similarly, for the dose of 40-mg/kg administered in children 3 to 23 months and 2 to 12 years of age, the CLp values were about 2.5-fold higher (geometric mean 1.11 mL/min/kg ±0.30, range 0.72-1.79, N=12 and 1.05 mL/min/kg, ± 0.21, range 0.79-1.38, N=8, respectively), as compared to healthy adults. The Figure 1 below depicts the effect of age on CLp in pediatrics.

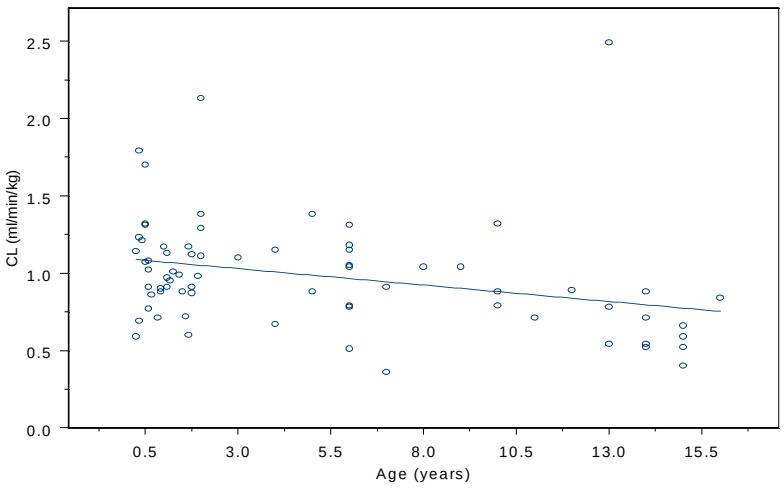
Table 1. CLp (mL/min/kg) for Total Ertapenem Following the Administration of Single IV Doses in Pediatric Patients 3 to 6, 7 to 12, 13 to 23 Months and 2 to 6, 7 to 12, 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g IV]).

Ertapenem Dose	Age Group	N	GM	CL_p GMR (Children/Adults)	90% CI
15 mg/kg	Adults[§]	16	0.429	--	
	7 to 12 years	4	0.819	1.911	(1.52, 2.40)
	2 to -6 years	4	1.193	2.783	(2.22, 3.50)
	13 to 23 months	4	0.833	1.944	(1.55, 2.44)
	7 to 12 months	4	0.854	1.993	(1.59, 2.50)
	3 to 6 months	4	1.180	2.753	(2.19, 3.46)
20 mg/kg[†]	Adults[§]	16	0.429	--	
	13 to 17 years	5	0.601	1.402	(1.09, 1.80)
	7 to 12 years	2	0.859	2.003	(1.39, 2.88)
	2 to 6 years	6	0.890	2.076	(1.65, 2.62)
	13 to 23 months	7	0.991	2.313	(1.86, 2.88)
	7 to 12 months	2	0.876	2.044	(1.42, 2.94)
	3 to 6 months	3	0.882	2.058	(1.52, 2.79)
40 mg/kg[‡]	Adults[§]	16	0.429	--	
	13 to 17 years	7	0.770	1.796	(1.44, 2.24)
	7 to 12 years	3	0.852	1.988	(1.46, 2.70)
	2 to 6 years	7	1.148	2.678	(2.15, 3.34)
	13 to 23 months	3	0.923	2.154	(1.64, 2.83)
	7 to 12 months	3	1.026	2.393	(1.76, 3.25)
	3 to 6 months	3	1.428	3.331	(2.45, 4.52)

[†] The 20-mg/kg was 1 g.
[‡] The 40-mg/kg was 2 g.
[§] Adults administered 1 g from Protocol 009.
CI = Confidence interval.
GM = Geometric mean.
GMR = Geometric mean ratio.

It is noted that the within the pediatric subgroups of 3 to 6 months, 7 to 12 months, 13 to 23 months, 2 to 6 yrs and 7 to 12 yrs the ertapenem CLp values were comparable.

Figure 1. Effect of age on plasma clearance in pediatrics (3 months to 17 years)



The plasma clearance on a per kg basis in adolescents (13 to 17 years) following the 20-mg/kg (geometric mean 0.60 mL/Min/kg ± 0.11, range 0.52-0.68) and 40 mg/kg (geometric mean 0.63 mL/Min/kg ± 0.19, range 0.40-2.49) dose were only slightly higher than that following a 1-g dose to healthy young adults (0.43 mL/min/kg).

A similar but slightly lower effect of age on volume of distribution at steady state (Vss) is also observed. The apparent volume of distribution at steady state (V_{ss}) of ertapenem is approximately 0.2 liter/kg in pediatric patients 3 months to 12 years of age, approximately 0.16 liter/kg in pediatric patients 13 to 17 years of age, and approximately 0.12 liter/kg in adults.

Mean plasma concentrations of total ertapenem in patients 3-months to 17 years following 15 mg/kg, 20 mg/kg, and 40 mg/kg are summarized in Tables 2 and 3, and the plasma-time concentration profiles are depicted in Figures 2-4 below:

Table 2. Mean Plasma Concentrations of Total Ertapenem Following Single 15-mg/kg,, 20-mg/kg and 40-mg/kg IV Doses Administered to 3- to 23-months and 2-to 12-Year-Old Pediatric Patients

Age Group (Dose)	Arithmetic Mean Plasma Concentrations (µg/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	--
(20-mg/kg)	126.8	87.6	58.7	28.4	--	12.0	3.4	0.4
(40-mg/kg)	199.1	144.1	95.7	58.0	--	20.2	7.7	0.6
2 to 12 years								
(15-mg/kg)	113.2	63.9	42.1	21.9	12.8	7.6	3.0	--
(20-mg/kg)	147.6	97.6	63.2	34.5	--	12.3	4.9	0.5
(40-mg/kg)	241.7	152.7	96.3	55.6	--	18.8	7.2	0.6

Table 3. Mean Plasma Concentrations of Total Ertapenem Following Single 20-mg/kg and 40-mg/kg IV Doses Administered to 13- to 17-Year-Old Pediatric Patients

Age Group (Dose)	Arithmetic Mean Plasma Concentrations (µg/mL)						
	0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr
13 to 17 years							
(20 mg/kg)	170.4	98.3	67.8	40.4	16.0	7.0	1.1
(40 mg/kg)	255.0	188.7	127.9	76.2	31.0	15.3	2.1

Table 4. 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.

	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

Figure 2. Mean Plasma Concentration Profiles of Total Ertapenem Following Single 15-mg/kg IV Doses Administered to 3- to 23-Month- and 2- to 12-Year-Old Pediatric Patients (Control From Protocol 009 [1-g IV Dose to Healthy Young Adults])

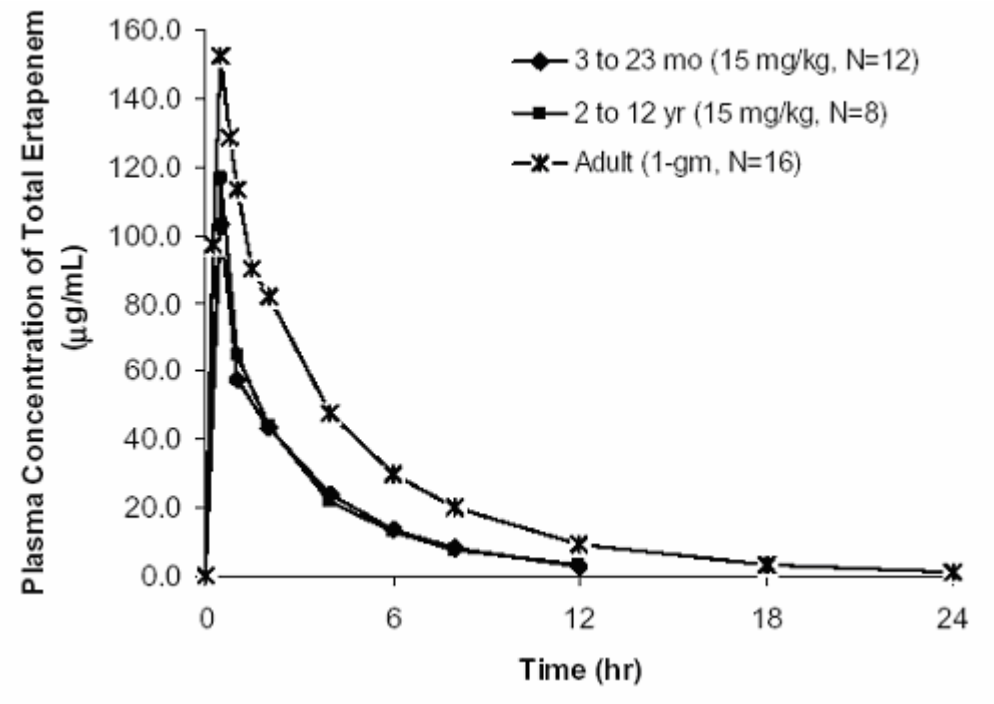


Figure 3. Mean Plasma Concentration Profiles of Total Ertapenem Following Single 20-mg/kg IV Doses Administered to 3- to 23-Month-, 2- to 12-Year-, and 13- to 17-Year-Old Pediatric Patients (Control From Protocol 009 [1-g IV Dose to Healthy Young Adults])

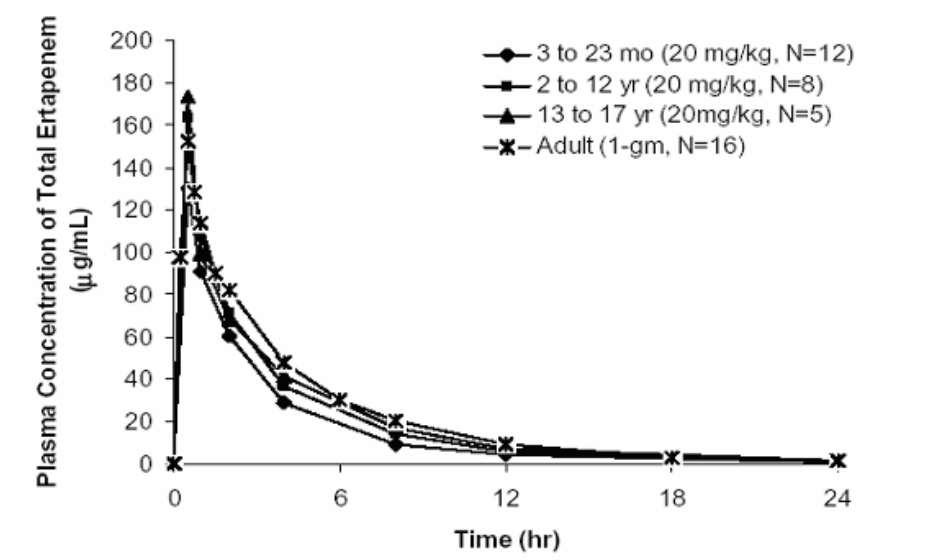
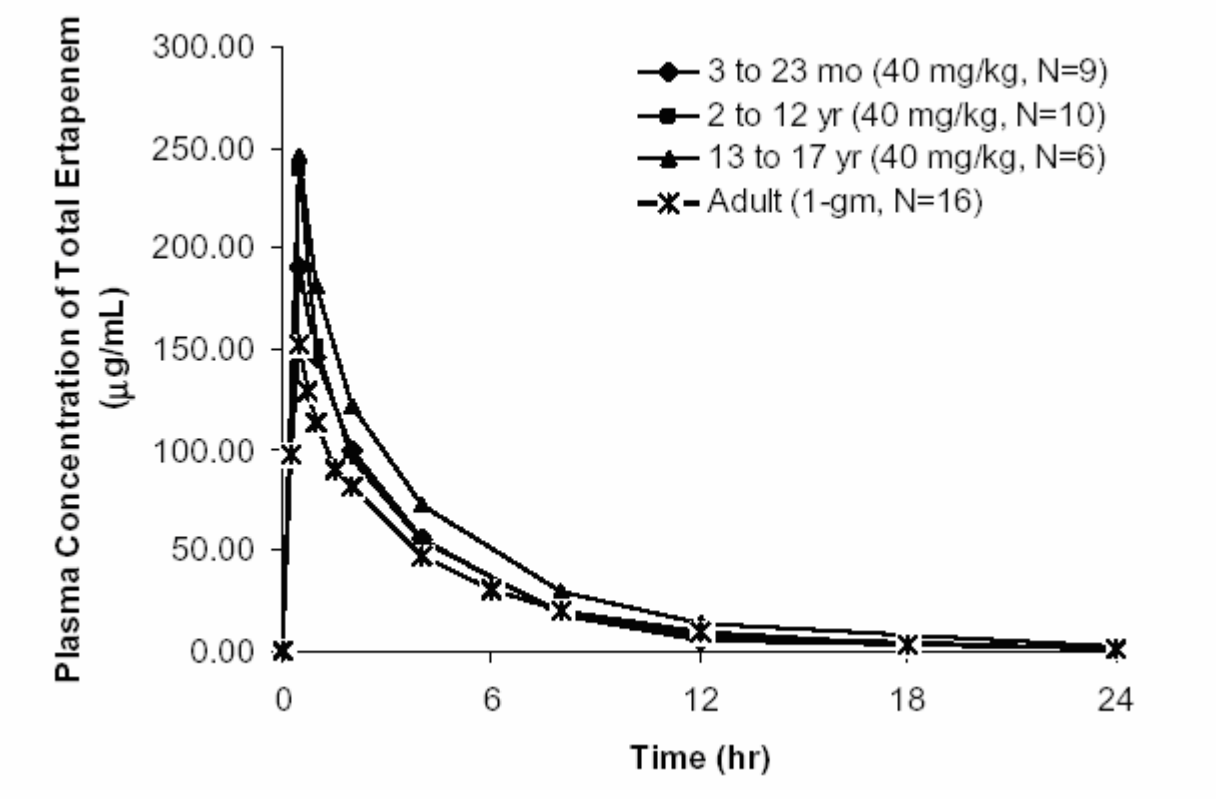


Figure 4. Mean Plasma Concentration Profiles of Total Ertapenem Following Single 40-mg/kg IV Doses Administered to 3- to 23-Month-, 2- to 12-Year-, and 13- to 17-Year-Old Pediatric Patients (Control From Protocol 009 [1-g IV Dose to Healthy Young Adults])



Extent of Exposure (AUC):

The gender and age group (aged 3 to 23 months, 2 to 12 years old, 13 to 17 years old, and the adults at 1 g from Protocol 009) factors at the 15-, 20-, and 40-mg/kg dose levels in children with regard to the pharmacokinetic parameters (natural log-transformed) were examined using an analysis of variance model (ANOVA) including gender and age group as class variables prior to the analysis.

For the natural log-transformed AUC (0-∞) for total ertapenem was doubled at 15-mg/kg dose level since the intended clinical use of 15-mg/kg IV was for bid dosing) and C12hr (C6hr was used at 15-mg/kg IV since it was intended for bid dosing).

Table 5. AUC(0-∞) (µg•hr/mL) for Total Ertapenem Following the Administration of Single IV Doses to Pediatric Patients 3 to 23 Months, 2 to 12 Years, and 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g IV])

Ertapenem Dose	Age Group	N	GM	$AUC_{(0-\infty)}$ GMR (Children/Adults)	90% CI
15 mg/kg†	Adults‖	16	568.400	--	
	2 to 12 years	8	505.861	0.890	(0.74, 1.07)
	3 to 23 months	12	529.925	0.932	(0.80, 1.09)
20 mg/kg‡	Adults‖	16	568.400	--	
	13 to 17 years	5	503.884	0.886	(0.71, 1.11)
	2 to 12 years	8	377.955	0.665	(0.55, 0.80)
	3 to 23 months	12	353.387	0.622	(0.53, 0.74)
40 mg/kg§	Adults‖	16	568.400	--	
	13 to 17 years	7	727.456	1.280	(1.04, 1.58)
	2 to 12 years	10	635.144	1.117	(0.93, 1.34)
	3 to 23 months	9	601.778	1.059	(0.87, 1.28)

† The $AUC_{(0-\infty)}$ was doubled at 15 mg/kg IV since the proposed administration of the 15-mg/kg dose was b.i.d.
‡ The maximum dose for 20 mg/kg was 1 g.
§ The maximum dose for 40 mg/kg was 2 g.
‖ Adults administered a single 1-g IV dose (Protocol 009).
CI = Confidence interval.
GM = Geometric mean.
GMR = Geometric mean ratio.

At the 20-mg/kg dose, the geometric mean (GM) AUC(0-∞) values in children 3 to 23 months (353.4 µg•hr/mL, ±100.3, N=12) and 2 to 12 years of age (378.0, µg•hr/mL ±147.7, N=8) were lower than those in young healthy adults (568.4 µg•hr/mL, ±74, N=16) receiving a 1 g dose of ertapenem. The AUC(0-∞) GMR of children/adults (with corresponding 90% CI) was 0.62 (0.53, 0.74) for 3- to 23-month and 0.67 (0.55, 0.80) for 2- to 12-year olds, and thus fell outside the pre-specified bounds specified by the primary hypothesis (Table 5).

At the 40-mg/kg dose, the GM AUC(0-∞) values in children 3 to 23 months (601.8 µg•hr/mL, ±156.1, N=9) and 2 to 12 years (859.2 µg•hr/mL, ±379.3, N=10) of age were generally comparable to those in young healthy adults receiving a 1 g dose of ertapenem (568.4 µg•hr/mL, ±74, N=14). The AUC(0-∞) GMR of children/adults (with corresponding 90% CI) was 1.06 (0.87, 1.28) for 3- to 23-month olds and 1.12 (0.93, 1.34) for 2- to 12-year olds (Table 5).

At the 15-mg/kg dose, the AUC(0-∞) values were 265.0 µg•hr/mL ±60.2 (range 190.7-426.5 µg•hr/mL, N=12) and 252.9 µg•hr/mL ±169.4 (range 180.8-692.9 µg•hr/mL, N=8), respectively for the 3-23 months and 2-12 years of age. When, the AUC(0-∞) values were doubled to simulate the proposed b.i.d. dosing in children 3 to 23 months and 2 to 12 years of age, the AUC(0-∞) GM values 529.9 µg•hr/mL, and 505.9 µg•hr/mL, respectively for the 3 to 23 months and 2 to 12 years of age were generally comparable to AUC(0-∞) GM value in young healthy adults receiving a 1g dose of ertapenem. The AUC(0-∞) GMR of children/adults (with corresponding 90% CI) was 0.93 (0.80, 1.09) for 3- to 23-month olds and 0.89 (0.74, 1.07) for 2- to 12-year olds (Table 5).

For adolescents aged 13 to 17 years, the ertapenem GM AUC(0-∞) values (503.9 µg•hr/mL ±98.5, N=5) after a 20-mg/kg dose were similar to that observed after a 1-g dose in healthy young adults . The ertapenem AUC(0-∞) GMR of adolescent/adults (with corresponding 90% CI) was 0.89 (0.71, 1.11) and fell within the pre-specified bounds (i.e., 0.67, 1.50) (Table 5). A somewhat higher value (727.5 µg•hr/mL, N=7) was achieved with a 40-mg/kg dose (Table 5).

Midpoint Plasma Concentration (C12hr)

The PK/PD parameter for predicting efficacy of ertapenem (carbapenems) is %T>MIC. Therefore, the plasma concentrations of ertapenem at the midpoint of the dosing interval for once-daily dosing, C12hr, provides a guide as to predicted efficacy in the treatment of aerobic pathogens. The current established highest aerobic susceptibility breakpoint as indicated in the ertapenem product circular is 2 µg/mL. The results of the analyses for C12hr of total ertapenem are given in Table 6 below.

Table 6. C12 hr (µg/mL) for Total Ertapenem Following the Administration of Single IV Doses in Pediatric Patients 3 to 23 Months, 2 to 12 Years, and 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g IV])

Ertapenem Dose	Age Group	N	GM	$C_{12\,hr}$ GMR (Children/Adults)	90% CI
20 mg/kg†	Adults§	16	8.890	--	
	13 to 17 years	6	6.891	0.775	(0.41, 1.48)
	2 to 12 years	9	3.300	0.371	(0.21, 0.65)
	3 to 23 months	15	2.583	0.291	(0.18, 0.47)
40 mg/kg‡	Adults§	16	8.890	--	
	13 to 17 years	7	11.265	1.267	(0.81, 1.97)
	2 to 12 years	9	6.601	0.743	(0.49, 1.12)
	3 to 23 months	13	5.871	0.660	(0.46, 0.95)

† The maximum dose for 20 mg/kg was 1 g.
‡ The maximum dose for 40 mg/kg was 2 g.
§ Adults administered a single 1-g IV dose (Protocol 009).
CI = Confidence interval.
GM = Geometric mean.
GMR = Geometric mean ratio.

At the 20-mg/kg dose, the GM C12hr values in children 3 to 23 months (N=15, 2.6 µg/mL ±2.4, range 0.35-9.97 µg/mL), 2 to 12 years (N=9, 3.3 µg/mL ±3.0, range 0.13-10.49 µg/mL) were generally lower, and the geometric mean ratios C12hr GMR of children/adults (with corresponding 90% CI) were 0.29 (0.18, 0.47) and 0.37 (0.21, 0.65) for 3- to 23-month-old and 2- to 12-year-old patients, respectively. Although GM C12hr values were above the susceptibility breakpoint of 2 µg/mL for aerobic pathogens in these pediatric patients, it is noted that 2 of the 15 children (13%) in the age group of 3-23 months had the C12hr value of 0.35 µg/mL each. Similarly, 2 of the 9 children (22%) in the age group of 2 to 12 years had C12hr values of 0.13 µg/mL and 1.96 µg/mL, respectively.

At the 40-mg/kg dose, the GM C12hr in children 3 to 23 months (N=13, 5.9 µg/mL ±5.6, range 1.24-14.12 µg/mL), and in children 2 to 12 years of age (N=9, 6.6 µg/mL ±3.3, range 4.03-12.65 µg/mL) were generally lower as compared to those in young healthy adults receiving a 1 g dose of ertapenem, but still higher than the susceptibility breakpoint of 2 µg/mL in all but one child in the 3-23 months age group.

The GM C12hr values in 13 to 17 years adolescents at the 20 mg/kg and 40 mg/kg were 6.9 µg/mL ±1.7 N=6, range = 5.4-9.7 µg/mL), 12.5 µg/mL ±12.6 (N=7, range 5.90-40.92 µg/mL).These values were generally comparable to those observed in young healthy adults receiving a 1 g dose of ertapenem (8.8 µg/mL).

Midpoint Plasma Concentration C6hr in 3 months to 12 years:

The primary purpose of administering single 15-mg/kg doses of ertapenem in children 3 to 23 months and 2 to 12 years of age in Protocol 028-04 was to investigate the plasma concentrations of ertapenem at the midpoint of the dosing interval (i.e., C6hr) for a proposed bid regimen, and compare the C6hr values to those observed in young healthy adults at the mid-point of the dosing interval (i.e., C12hr) following a 1 g dose. The C6 values are based on (logarithmic) interpolation of the plasma concentration values obtained 4 and 8 hours postdose. The results of the analyses of C6hr for total ertapenem are given in Table 7.

At the 15-mg/kg dose, GM C6hr values for the age group of 3 to 23 months (12.7 µg/mL ± 4.1, N=12, range 4.44-19.67 µg/mL), and of 2 to 12 years (12.7 µg/mL ± 9.6, N=8, range 5.72-34.39 µg/mL) were well above the susceptibility breakpoint value of 2 µg/mL, and were generally comparable to higher than the concentration at the midpoint (C12hr) of the dosing interval for the 1 g dose administered to young healthy adults.

Table 7. C6 hr (µg/mL) of Total Ertapenem in Pediatric Patients 3 to 23 Months and 2 to 12 Years of Age Following Administration of a Single 15-mg/kg Dose Versus C12 hr (µg/mL) in Young Healthy Adult Subjects Following Administration of a Single 1 g Dose of Ertapenem (Control From Protocol 009)

Age Group	N	GM	$C_{6\ hr}$ GMR (Children/Adults)	90% CI
Adults	16	8.890	--	
2 to 12 years	8	10.700	1.204	(0.88, 1.64)
3 to 23 months	12	12.723	1.431	(1.09, 1.88)

CI = Confidence interval.
GM = Geometric mean.
GMR = Geometric mean ratio.

Concentration at the End of Infusion (Ceoi)/Maximal Concentration:

Ceoi is expected to assist in guiding the proposed dose in pediatric patients so that exceedingly high maximal concentrations can be avoided, which, in theory, might increase the incidence of peak-related adverse experiences. The results of the analyses for Ceoi for total ertapenem are given in Table 8.

At the 20-mg/kg dose, in children 3 to 23 months of age, the GM Ceoi (125.0 µg/mL, ± 21.9, range 92.3-162.2 µg/mL, N=15) were slightly lower compared to those observed in healthy young adults receiving a 1 g dose (153.4 µg/mL). In children 2 to 12 years of age, the GM Ceoi (145.0 µg/mL, ± 28.5, range 96.0-196.0, µg/mL N=8) was generally comparable to that observed in healthy young adults. Similarly, in children 13 to 17 years of age, the GM Ceoi (165.4 µg/mL, ± 47.9, range 126.9-200.7 µg/mL, N=4) was generally comparable to that observed in healthy adults.

At the 40-mg/kg dose, the GM Ceoi values in all pediatric age groups were generally higher as compared to that in healthy adults receiving a 1g dose (Table 8).

At the 15-mg/kg dose, as expected, the GM Ceoi values in children 3 to 23 months and 2 to 12 years were lower (98.5 µg/mL, ± 42.4, range 71.5 -113.0 µg/mL, N=12, and 103.9 µg/mL, ± 58.6, range 90.4 -252.1 µg/mL, N=8, respectively) as compared to healthy young adults (Table 8).

Table 8. Ceoi (µg/mL) for Total Ertapenem Following the Administration of Single IV Doses in Pediatric Patients 3 to 23 Months and 2 to 12, and 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g IV])

Ertapenem Dose	Age Group	N	GM	C_{eoi} GMR (Children/Adults)	90% CI
15 mg/kg	Adults§	16	153.384	--	
	2 to 12 years	8	103.905	0.677	(0.55, 0.83)
	3 to 23 months	12	98.522	0.642	(0.54, 0.77)
20 mg/kg†	Adults§	16	153.384	--	
	13 to 17 years	5	165.382	1.078	(0.92, 1.26)
	2 to 12 years	8	145.030	0.946	(0.83, 1.08)
	3 to 23 months	15	125.020	0.815	(0.73, 0.91)
40 mg/kg‡	Adults§	16	153.384	--	
	13 to 17 years	7	205.465	1.340	(1.08, 1.66)
	2 to 12 years	10	237.696	1.550	(1.28, 1.88)
	3 to 23 months	13	193.193	1.260	(1.05, 1.51)

† The maximum dose for 20-mg/kg was 1 g.
‡ The maximum dose for 40-mg/kg was 2 g.
§ Adults administered a single 1-g IV dose (Protocol 009).
CI = Confidence interval.
GM = Geometric mean.
GMR = Geometric mean ratio.

Half-Life (t1/2):

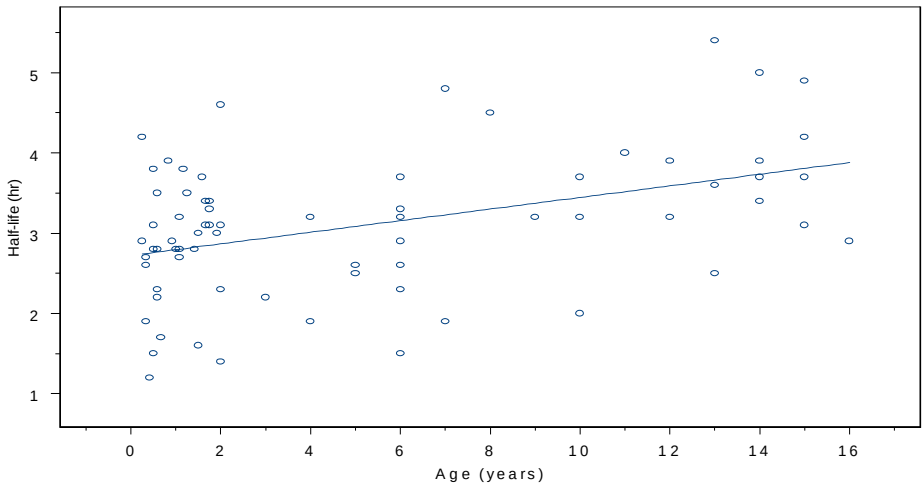
The half-life (t½) for total ertapenem at the 15-, 20-, and 40-mg/kg dose levels for patients 3 months to 17 years of age is given in Table 9 and Figure 5. The harmonic mean t½ in 13- to 17-year-old patients was comparable to that observed in healthy young subjects. Mean t½ was lower in 3- to 23-month- and 2- to 12-year-old patients than that observed in adolescents or young healthy adults.

Table 9. Harmonic Mean (Pseudo SD) Half-Life (hours) of Total Ertapenem Following the Administration of Single IV Doses in Pediatric Patients 3 to 23 Months, 2 to 12, and 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g and 2 g IV])

Age Group	Ertapenem Dose		
	15 mg/kg	20 mg/kg	40 mg/kg
3 to 23 months	2.5 (1.1)	2.9 (1.0)	2.7 (0.5)
2 to 12 years	2.4 (1.0)	2.8 (1.3)	2.9 (0.5)
13 to 17 years	--	4.0 (0.8)	3.7 (0.7)
Adults	--	3.8 (0.5)†	3.8 (0.5)‡

† Half-life following administration of a single 1-g dose.
‡ Half-life following administration of a single 2-g dose.
SD = Standard deviation.

Figure 5.Effect of age on half-life on ertapenem in the pediatric population



Percentage of Dose in Urinary Excretion (Fe) and Renal Clearance (CLR):

The mean (SD) Fe (% of dose excreted in urine) and the CLR (renal clearance on per kg basis) of total ertapenem following single IV doses in pediatric patients 2 to 6 years, 7 to 12 years, and 13 to 17 years of age are given in Table 10. Note that these data are based on small numbers of patients in each group. The mean Fe are based on even a smaller number of patients because the urine collection was incomplete. For the purpose of comparison, the mean (SD) Fe and CLR values in healthy adults following 1-g or 2-g doses from Protocol 009 are also included. The Fe of ertapenem in pediatric patients appears to be generally comparable to that observed in healthy adult subjects. The CLR was observed to be approximately 2-fold higher in 2- to 12-year-old patients and approximately 1.5-fold higher in 13- to 17-year-old patients as compared to the observed values in healthy adult subjects.

The values for <2-year-old patients are variable and quite low for a few of the patients (10 to 14% of dose recovered in urine).

Table 10. Mean (SD) Fe and CLR of Ertapenem Following Single IV Doses in Pediatric Patients 2 to 6, 7 to 12, and 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g and 2 g IV])

Age Group	N	$F_{e\ (0\text{-}24\ hr)}$ (%)	N	CL_R (mL/min/kg)
2 to 6 Years	3	58 (7)	7	0.48 (0.19)
7 to 12 Years	6	56 (17)	7	0.48 (0.16)
13 to 17 Years	7	47 (6)	8	0.31 (0.10)
Adults	16	44 (14)	16	0.21 (0.09)

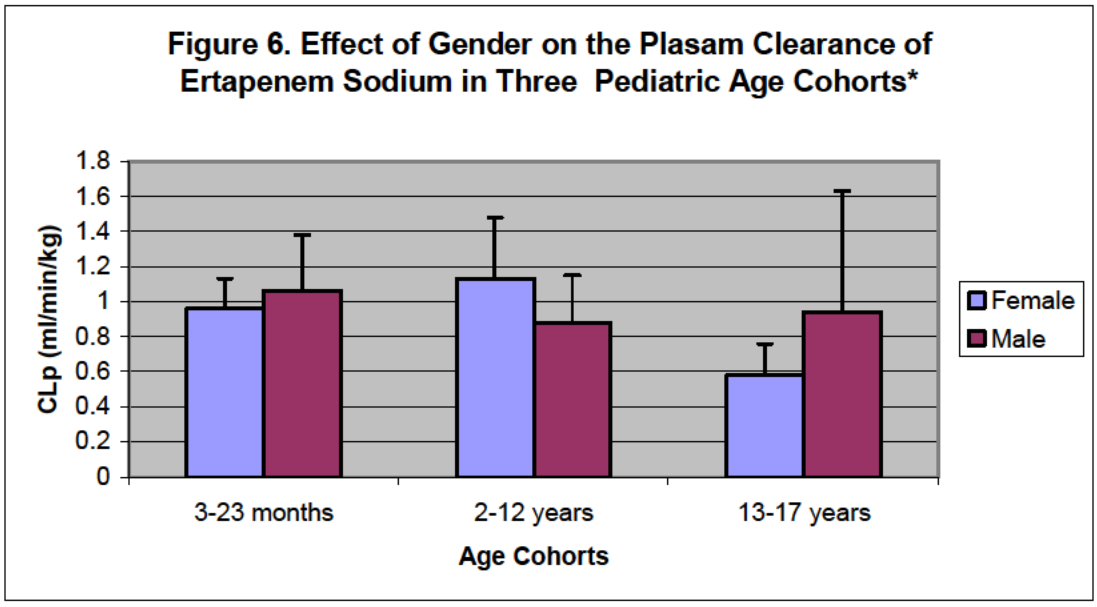
2.3.1.2. What is the influence of gender on the pharmacokinetics of ertapenem in children?

With regards to gender, there was no statistical evidence of a gender effect at any of the 3 dose levels, 15-, 20- and 40-mg/kg in the pediatric population. The respective p-values were 0.5787, 0.3384, and 0.2026 for log AUC(0-∞); and 0.3444, 0.0904, and 0.7571 for log C12hr.

For the Ceoi, at the 15-mg/kg and 20-mg/kg dose levels, there was no statistical evidence of gender effect (p-values = 0.7835 and 0.8793 for log-Ceoi at15 mg/kg and 20 mg/kg, respectively). At the 40-mg/kg dose level in children, the analysis indicated that there was some evidence of a gender effect (p-value = 0.0362). However, this was not considered to be clinically important.

For the CLp, at the 15-mg/kg and 20-mg/kg dose levels in children, the analysis indicated that gender was marginally significant (p-value = 0.0655 and 0.0573 for log- CLp at dose levels 15- and 20-mg/kg respectively). At the 40-mg/kg dose level (in children), there was no statistical evidence of a gender effect (p-value = 0.7490).

As shown in the following figure, there is no significant gender effect among three age cohorts on the clearance of ertapenem when data for all doses were combined.



**clearance for 3 to 23 months and 2 to 12 years includes data for 15, 20 and 40 mg/kg doses; clearance 13 to 17 years includes data for 20 and 40 mg/kg doses.*

2.3.1.3. What is the Pharmacokinetics of Unbound Ertapenem?

The mean (SD) pharmacokinetic parameters for plasma unbound ertapenem following the administration of single doses of 20-mg/kg and 40-mg/kg dose is given in Table 11 below. The mean and (SD) values are based on a small number of patients in each age group and, therefore, must be interpreted with caution. Although not measured here due to restrictions in blood sampling, both Ceoi and C12hr of unbound ertapenem following a 15-mg/kg dose in the less than 13-year-old patients would be expected to be somewhat lower than the values reported here following the 20-mg/kg dose. The AUC(0-∞) of unbound ertapenem appeared similar in patients 13 to 17 years of age at the 20-mg/kg dose as compared to healthy young adults receiving a single 1-g dose of ertapenem (36.2 µg•hr/mL in 13- to 17-year olds versus 33.2 µg•hr/mL in adults). C12hr also appeared similar (0.37 µg/mL in 13- to 17-year olds versus 0.41 µg/mL in adults). The Ceoi was 19.9 µg/mL in 13- to 17-year olds versus 12.9 µg/mL in adults receiving a 1-g dose. This is consistent with a slightly higher fraction unbound at the end of infusion (Fueoi) in 13- to 17-year olds as compared to adults (0.12 versus 0.08).

Table 11. Mean (SD) Pharmacokinetic Parameters of Unbound Ertapenem Following Single IV Doses in Pediatric Patients 3 to 23 Months, 2 to 6, 7 to 12, and 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g and 2 g IV])

Age Group/ (N)	Dose (mg/kg)	Dose-Adjusted C_{eoi} (µg/mL)	Dose-Adjusted C_{1hr} (µg/mL)	Dose-Adjusted C_{12hr} (µg/mL)	Fu_{eoi}	Fu_{1hr}	Fu_{12hr}	Dose-Adjusted AUC (µg•hr/mL)	CL_P (mL/min/kg)
3 to 23 months									
(2 to 5)	20	15.4 (2.6)	NA	0.28 (0.38)	0.12 (0.03)	NA	0.10 (0.02)	NA	NA
(6)	40	33.0 (10.8)	NA	0.50 (0.31)	0.17 (0.06)	NA	0.05 (0.02)	NA	NA
2 to 6 years									
(2 to 5)	20	17.7 (5.1)	9.4 (2.4)	0.21 (0.31)	0.13 (0.06)	0.10 (0.04)	0.05 (0.01)	NA	NA
(1 to 3)	40	44.9 (15.0)	18.2 (NA)	0.21 (NA)	0.19 (0.06)	0.14 (NA)	0.05 (NA)	NA	NA
7 to 12 years									
(2 to 3)	20	14.2 (2.6)	7.9 (0.04)	0.65 (0.49)	0.09 (0.02)	0.08 (0.01)	0.10 (0.08)	29.0 (2.8)	11.6 (1.1)
(2 to 3)	40	42.7 (2.0)	21.1 (4.7)	0.55 (0.09)	0.17 (0.02)	0.12 (0.02)	0.05 (0.00)	72.5 (11.6)	9.3 (1.5)
13 to 17 years									
(1 to 4)	20	19.9 (5.1)	11.1 (NA)	0.37 (0.10)	0.12 (0.02)	0.10 (NA)	0.05 (0.01)	36.2 (8.0)	9.4 (2.1)
(5 to 6)	40	61.5 (25.4)	27.3 (11.5)	0.84 (0.58)	0.23 (0.07)	0.14 (0.03)	0.06 (0.02)	98.8 (43.9)	5.9 (1.3)
Adults									
(16)	1 g	12.9 (3.2)	7.8 (1.9)	0.41 (0.16)	0.08 (0.01)	0.07 (0.01)	0.04 (0.01)	33.2 (5.5)	7.5 (1.4)
(16)	2 g	43.3 (14.8)	20.8 (5.7)	0.73 (0.20)	0.15 (0.04)	0.10 (0.02)	0.04 (0.01)	76.6 (13.2)	6.5 (1.0)

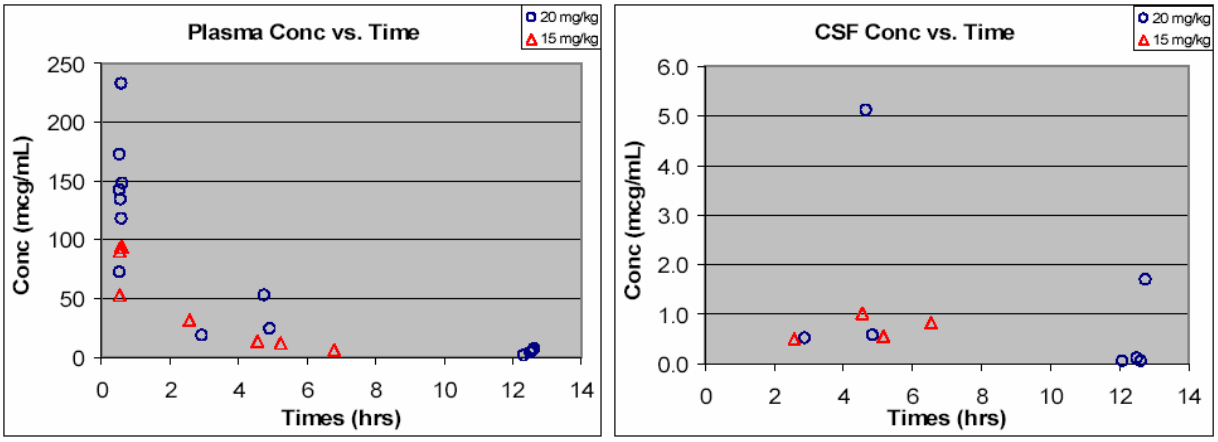
The mean (SD) values for pediatric groups, especially for the younger ones, must be interpreted with caution since they are based on very small numbers of patients.
AUC = $AUC_{(0-\infty)}$
NA = Not available.
Values <LOQ were set to zero.

2.3.1.4. What is the Degree of Penetration of Etrapenem in Cerebral-Spinal Fluid (CSF)?

The studies under Protocol 031 (US) and P032 (Outside US) were conducted to evaluate CSF penetration of ertapenem in clinically stable children and adolescents aged ≥3 months to ≤17 yrs who were receiving intravenous cefotaxime (200 mg/kg IV q8h) or other antibiotic therapy for bacterial meningitis. A single intravenous 15 mg/kg or 20 mg/kg dose of ertapenem (maximum 1 gram) was infused over 30 min as close as possible to the dosing interval midpoint for each patient's ongoing cefotaxime or other appropriate antibiotic therapy. Ertapenem was administered on day 2 or 3 of therapy for meningitis. Of the 13 patients entered in the study, 11 were considered evaluable (i.e. received ertapenem and had CSF samples collected for ertapenem concentration determination).

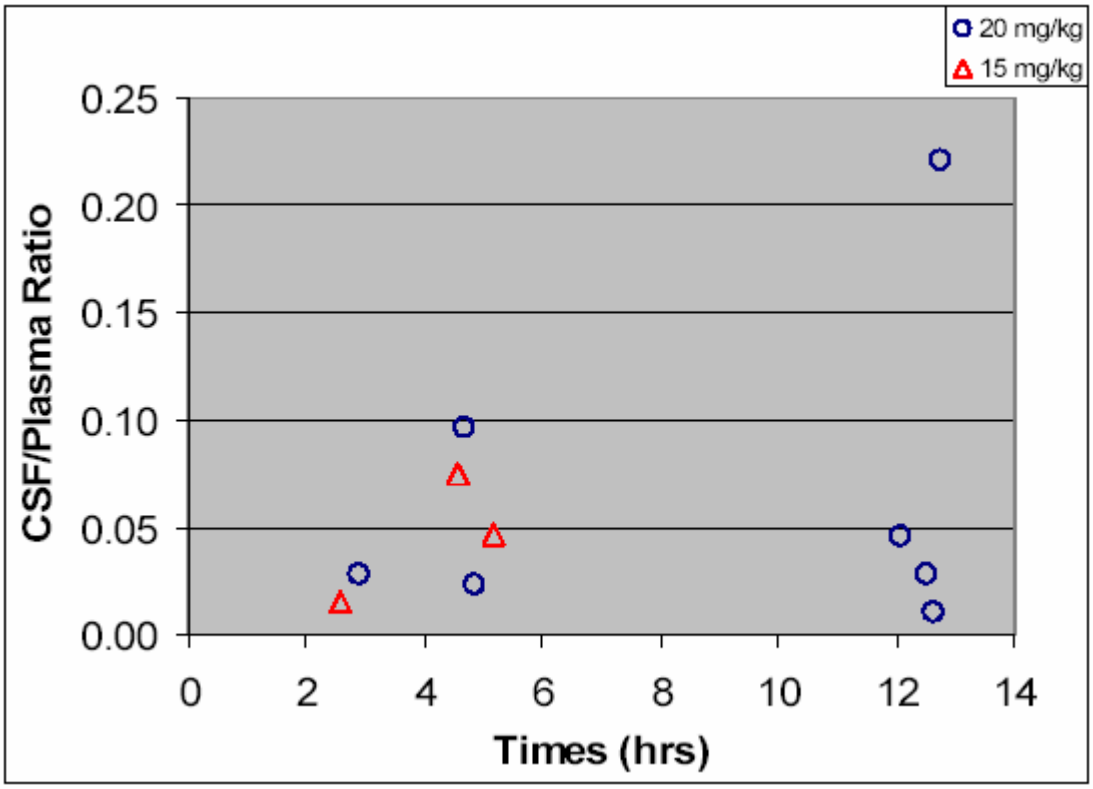
The concentration of ertapenem at the end of infusion (0.5 hrs) and from corresponding plasma and CSF samples obtained at 2, 4, 6, and 12 hrs are shown in Figure 7 below:

Figure 7. Individual plasma (left plot) and CSF (right plot) concentrations (mcg/mL) for all patients with evaluable data (n=11) [Courtesy: Dr. Charles Bonapace's Review of IND 48,486/S-471, Nov 07, 2003]



The mean (SD) plasma ertapenem concentrations at the end of infusion were 145.9 (49.5) µg/mL for the 20 mg/kg cohort and 82.7 (19.8) µg/mL for the 15 mg/kg cohort. The median CSF concentrations were 0.53 µg/mL and 0.70 µg/mL for the 15 mg/kg and 20 mg/kg cohorts, respectively. Except for two patients in which the CSF concentration exceeded 1 µg/mL (5.12 µg/mL at 4.67 hrs and 1.69 µg/mL at 12.75 hrs, both in the 20 mg/kg cohort), the CSF concentrations of ertapenem did not exceed 1 µg/mL. The individual CSF/plasma ratios ranged from 0.01 to 0.22 following administration of 20 mg/kg and 0.02 to 0.07 following administration of 15 mg/kg (Figure 8).

Figure 7. Individual plasma/CSF concentration ratios for all patients with evaluable data (n=10) [Courtesy: Dr. Charles Bonapace's Review of IND 48,486/S-471, Nov 07, 2003]



These results of the CSF penetration study showed insufficient CSF concentrations to cover all relevant pathogens and in the Final Amended PWR 04 May, 2004 the FDA concurred with the removal of the pediatric meningitis efficacy study as a requirement for the ertapenem pediatric program. Additionally, based on this PK/PD relationship (or lack of it) the following recommendation has been made by the reviewer to be included in the proposed labeling, where appropriate:

INVANZ is NOT INDICATED in the treatment of meningitis in the pediatric population.

2.4. Effect of Extrinsic Factors

Not Applicable

2.5. General Biopharmaceutics

Biopharmaceutics properties of Ivanz are provided in CPB Review for NDA 21-337; no additional information was provided in the current submission. It is noted that the formulation is (b) (4) for intravenous injection allowing easy dose-adjustment based on body weight.

2.6. Analytical

Plasma samples collected were analyzed for total and unbound ertapenem, and the urine samples collected were analyzed for total ertapenem (b) (4) The analytical assay used a validated HPLC/ UV method. The lower limit of quantitation was 0.125 µg/mL for plasma total drug assay, 0.25 µg/mL for plasma unbound drug assay, and 2.5 µg/mL for urine total drug assay. The accuracy and precision were acceptable.

3. Detailed Labeling Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB/DPE-2) has reviewed the package insert labeling for Ivanz and finds it acceptable pending the following revision:

(~~Strikethrough text~~ is recommended to be deleted and **underlined text** is recommended to be added.)

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.

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 (b) (4) (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. (b) (4)

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.

INDICATIONS AND USAGE

INVANZ is indicated for the treatment of patients with the following moderate to severe infections caused by susceptible strains 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 due to *Staphylococcus aureus* (methicillin susceptible strains 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.*

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.

PRECAUTIONS

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.

4. Appendices
4.1. Proposed Labeling (Annotated)

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4.2. INDIVIDUAL STUDY REPORT

4.2.1. Study Protocol 028: **Multicenter Phase 1, open-label, intravenous study to evaluate the plasma concentration profiles of MK-0826 in patients aged 3 months through 17 years.**

Study Objectives: This study was designed to evaluate the safety, tolerability, and pharmacokinetics of ertapenem in patients across the 3 main age strata, including 3 to 23 months, 2 to 12 years, and 13 to 17 years, as subgroups consisting of 3 to 6 months, 7 to 12 months, 13 to 23 months, 2 to 6 years, 7 to 12 years, and 13 to 17 years of age.

Study Dates: Started: Mar 22, 2000 Completed: Feb 19, 2003
Principal Investigator: Gary Herman, M.D.
Study Subjects: Patients who entered into this study participated at 1 of the 8 study sites. A total of 84 patients were enrolled in this study as given in the following Table. One patient, AN 0111, was discontinued after the completion of dosing but prior to the completion of all post study procedures. This patient was not included in the complete pharmacokinetic analyses but was included in the safety analyses. The inclusion and exclusion criteria are provided in section 5.3.1 and 5.3.2, respectively.

Number of Patients Enrolled by Dose and Age Group

Age	Ertapenem Dose Level			Total
	15 mg/kg	20 mg/kg	40 mg/kg	
3 to 23 Months				
3 to 6 months	5	4	4	13
7 to 12 months	3	4	5	12
13 to 23 months	4	8	6	18
2 to 12 Years				
2 to 6 years	4	6	7	17
7 to 12 years	4	3	4	11
13 to 17 Years†	--	6	7	13
Total	20	31	33	84

† Patients 13 to 17 years of age did not receive the 15-mg/kg dose of ertapenem.

Data Source: [4.1.1; 4.3.1]

Patients' disposition is given in the following Table:

		3 to 23 Months	2 to 12 Years	13 to 17 Years
ENTERED: Total	84	43	28	13
Male (age range)	42 (3 months to 15 years)	24 (3 to 23)	10 (4 to 11)	8 (13 to 16)
Female (age range)	42 (4 months to 15 years)	19 (4 to 22)	18 (2 to 12)	5 (14 to 15)
COMPLETED:	83			
DISCONTINUED:	1			
Other	1			

Treatment

In protocols 028-01, 028-02, and 028-03, children or adolescents 3 months to 17 years of age received a single IV 20-mg/kg or 40-mg/kg dose of ertapenem administered via an infusion pump over 30 minutes to assess the pharmacokinetics of the 20-mg/kg and 40-mg/kg dose levels. The 40-mg/kg cohort for each age group was initiated only after enrollment was completed and safety and tolerability were demonstrated for that cohort at 20 mg/kg. The maximum dose was capped at 1 g and 2 g for the patients receiving 20 mg/kg and 40 mg/kg doses, respectively.

In Protocol 028-04, children 3 months to 12 years of age received 15-mg/kg dose of ertapenem administered via an infusion pump over 30 minutes to assess the suitability of the 15-mg/kg b.i.d. dosing regimen. There was a minimum of at least 4 clinically stable patients in each of the following subgroups: 3 to 6 months, 7 to 12 months, 13 to 23 months, 2 to 6 years, and 7 to 12 years.

The following ertapenem formulations and clinical lot no. were used in the study:

Formulation No.	Log No.
0826 HLS014A017	WP-G601 and WG-G805
0826 HLS014A023	WP-H481
0826 HLS014A007	WP-J566
0826 HLS014A015	WP-K573

Pharmacokinetics
Blood samples collected at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours postdose were assayed for total and unbound ertapenem for determination of plasma ertapenem pharmacokinetic parameters. Urine samples collected up to 24 hours postdose were assayed for ertapenem for the determination of urinary excretion of unchanged drug.
Protocol Deviations
No major protocol deviations were reported.
Bioanalytical Methods
Plasma samples collected were analyzed for total and unbound ertapenem and the urine samples collected were analyzed for total ertapenem (b) (4) The analytical method used HPLC with UV detection. The lower limit of quantitation was 0.125 µg/mL for plasma total drug assay, 0.25 µg/mL for plasma unbound drug assay, and 2.5 µg/mL for urine total drug assay. The details of the assay procedures are provided in the bioanalytical report [2.1].
Statistical and Analytical Plans
Log-transformed AUC(0-∞) values for total ertapenem at various dose levels in children were analyzed using an analysis of variance (ANOVA) model with age factor (aged 3 to 23 months, 2 to 12 years, 13 to 17 years old, and the healthy adults at 1 g from Protocol 009 [historical control]). The geometric means (GMs) and 90% confidence intervals (CIs) for geometric mean ratios (GMRs) (children/adults) were calculated to evaluate the equivalence between different age groups in children and healthy adults in the historical control. For the secondary pharmacokinetic variables, such as Ceoi, CLp, and C12 hr, the same method stated above was applied. The exploratory analyses for various pharmacokinetic parameters with age group (3 to 6 months, 7 to 12 months, 13 to 23 months, 2 to 6 years, 7 to 12 years, and 13 to 17 years) at various dose levels were conducted using the same method stated above.

Results Mean plasma concentrations of total ertapenem in patients 3-months to 17 years following 15 mg/kg, 20 mg/kg, and 40 mg/kg are summarized in Tables 1 and 2 below. Plasma-Concentration Time profiles are depicted in Figures 1-3. Results of relevant PK parameters summarized in the subsequent Tables.

Table 1. Mean Plasma Concentrations of Total Ertapenem Following Single 15-mg/kg,, 20-mg/kg and 40-mg/kg IV Doses Administered to 3- to 23-months and 2-to 12-Year-Old Pediatric Patients

Age Group (Dose)	Arithmetic Mean Plasma Concentrations (µg/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	--
(20-mg/kg)	126.8	87.6	58.7	28.4	--	12.0	3.4	0.4
(40-mg/kg)	199.1	144.1	95.7	58.0	--	20.2	7.7	0.6
2 to 12 years								
(15-mg/kg)	113.2	63.9	42.1	21.9	12.8	7.6	3.0	--
(20-mg/kg)	147.6	97.6	63.2	34.5	--	12.3	4.9	0.5
(40-mg/kg)	241.7	152.7	96.3	55.6	--	18.8	7.2	0.6

Data Source: [2.1]

Table 2. Mean Plasma Concentrations of Total Ertapenem Following Single 20-mg/kg and 40-mg/kg IV Doses Administered to 13- to 17-Year-Old Pediatric Patients

Age Group (Dose)	Arithmetic Mean Plasma Concentrations (µg/mL)						
	0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr
13 to 17 years							
(20 mg/kg)	170.4	98.3	67.8	40.4	16.0	7.0	1.1
(40 mg/kg)	255.0	188.7	127.9	76.2	31.0	15.3	2.1

Data Source: [2.1]

Figure 1. Mean Plasma Concentration Profiles of Total Ertapenem Following Single 15-mg/kg IV Doses Administered to 3- to 23-Month- and 2- to 12-Year-Old Pediatric Patients (Control From Protocol 009 [1-g IV Dose to Healthy Young Adults])

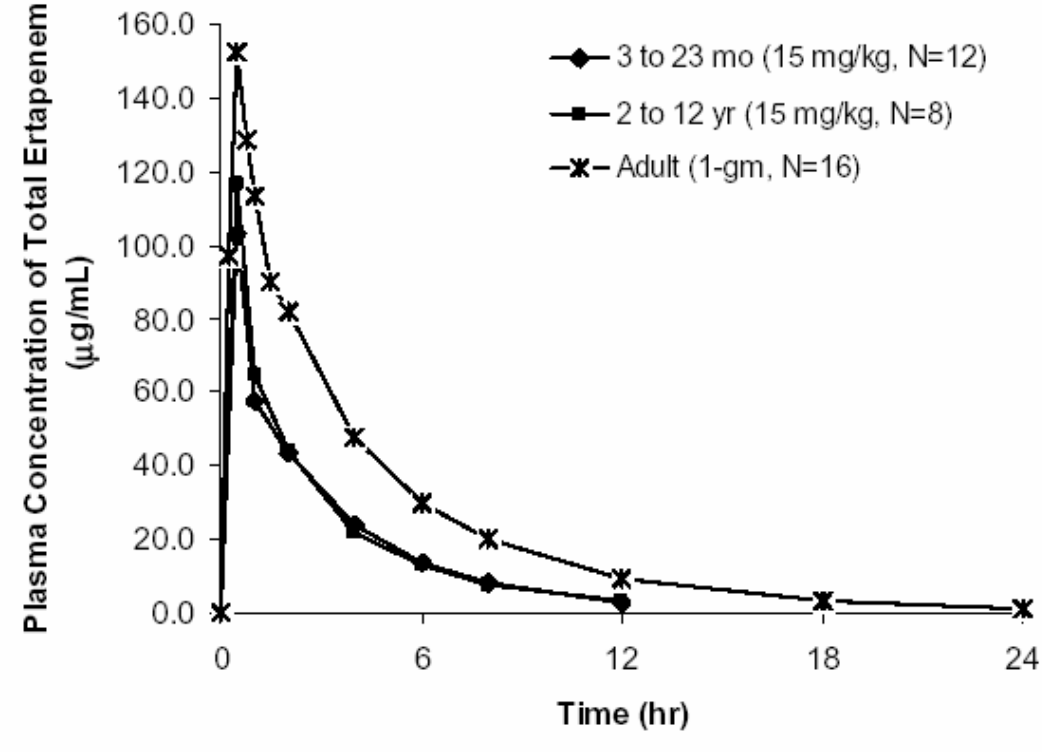


Figure 2. Mean Plasma Concentration Profiles of Total Ertapenem Following Single 20-mg/kg IV Doses Administered to 3- to 23-Month-, 2- to 12-Year-, and 13- to 17-Year-Old Pediatric Patients (Control From Protocol 009 [1-g IV Dose to Healthy Young Adults])

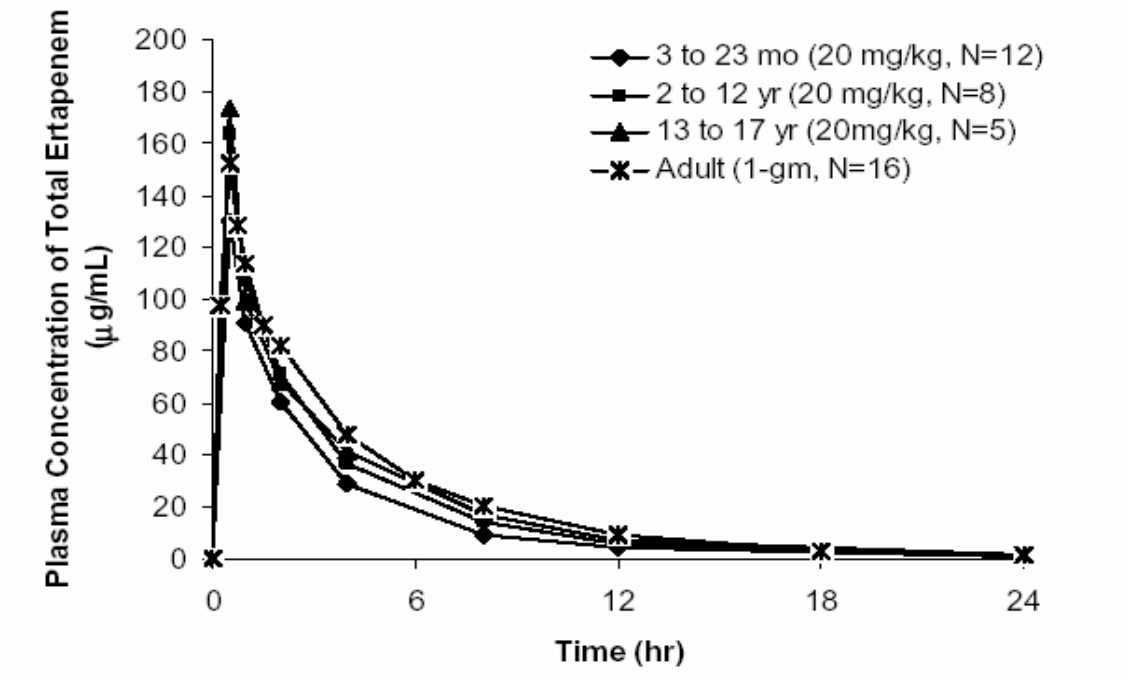
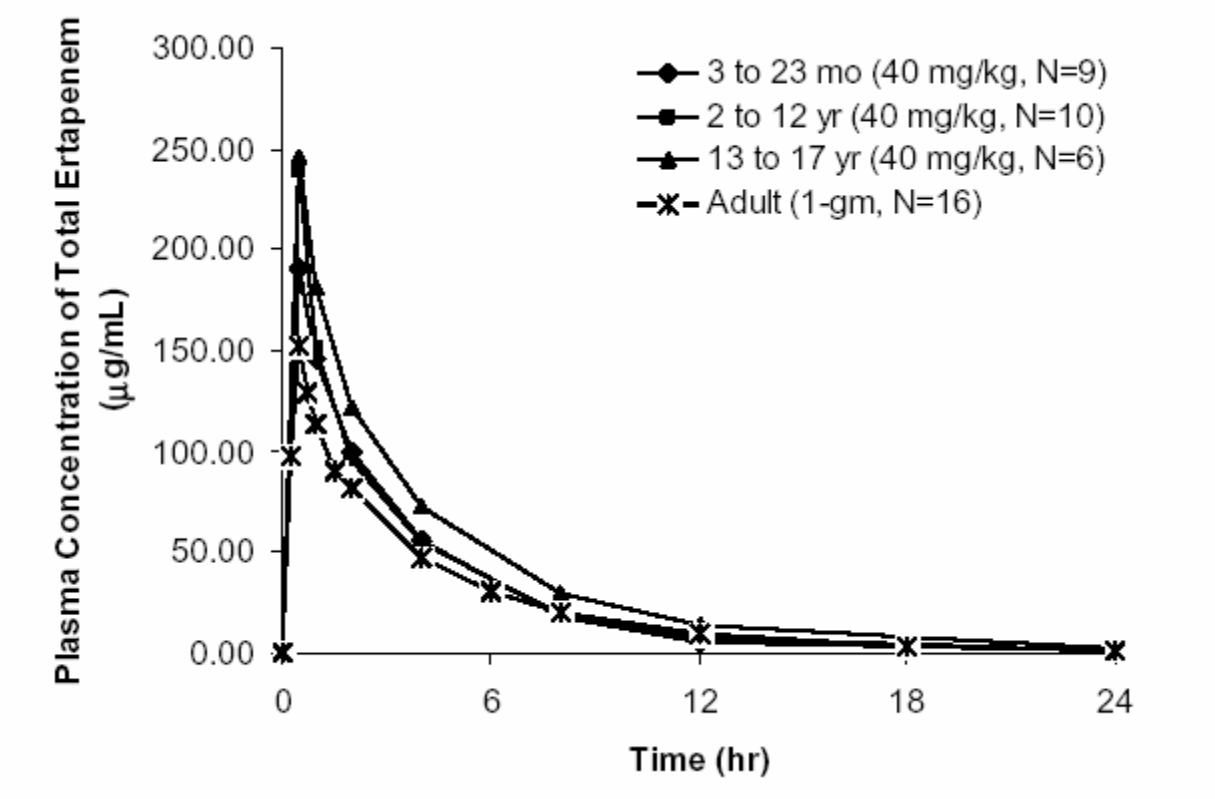


Figure 3. Mean Plasma Concentration Profiles of Total Ertapenem Following Single 40-mg/kg IV Doses Administered to 3- to 23-Month-, 2- to 12-Year-, and 13- to 17-Year-Old Pediatric Patients (Control From Protocol 009 [1-g IV Dose to Healthy Young Adults])



AUC(0-∞) for 20-mg/kg, 40-mg/kg and 15 mg/kg bid (Tables 3 and 4)

- At the 20-mg/kg dose, the GM AUC(0-∞) values in children 3 to 23 months and 2 to 12 years of age were somewhat lower than those in young healthy adults receiving a 1-g dose of ertapenem. The AUC(0-∞) GMR of children/adults (with corresponding 90% CI) were 0.62 (0.53, 0.74) for 3 to 23 months and 0.67 (0.55, 0.80) for 2 to 12 years.

- At the 40-mg/kg dose, the GM AUC(0-∞) values in children 3 to 23 months and 2 to 12 years of age were comparable to those in young healthy adults receiving a 1-g dose of ertapenem. The AUC(0-8) GMR of children/adults (with corresponding 90% CI) were 1.06 (0.87, 1.28) for 3- to 23-month olds and 1.12 (0.93, 1.34) for 2- to 12-year olds.

At the 15-mg/kg dose, the GM AUC(0-∞)) values (doubled to simulate the proposed 15-mg/kg b.i.d. dosing, i.e., representing a 30 mg/kg/day exposure) in children 3 to 23 months and 2 to 12 years of age were generally comparable to AUC(0-8) values in young healthy adults receiving a 1-g dose of ertapenem. The AUC(0-∞) GMR of children/adults (with corresponding 90% CI) was 0.93 (0.80, 1.09) for 3- to 23-month olds and 0.89 (0.74, 1.07) for 2- to 12-year olds.

Table 3. AUC(0-∞) (µg•hr/mL)for Total Ertapenem Following the Administration of Single IV Doses to Pediatric Patients 3 to 23 Months, 2 to 12 Years, and 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g IV])

Ertapenem Dose	Age Group	N	GM	$AUC_{(0-\infty)}$ GMR (Children/Adults)	90% CI
15 mg/kg†	Adults‖	16	568.400	--	
	2 to 12 years	8	505.861	0.890	(0.74, 1.07)
	3 to 23 months	12	529.925	0.932	(0.80, 1.09)
20 mg/kg‡	Adults‖	16	568.400	--	
	13 to 17 years	5	503.884	0.886	(0.71, 1.11)
	2 to 12 years	8	377.955	0.665	(0.55, 0.80)
	3 to 23 months	12	353.387	0.622	(0.53, 0.74)
40 mg/kg§	Adults‖	16	568.400	--	
	13 to 17 years	7	727.456	1.280	(1.04, 1.58)
	2 to 12 years	10	635.144	1.117	(0.93, 1.34)
	3 to 23 months	9	601.778	1.059	(0.87, 1.28)

† The $AUC_{(0-\infty)}$ was doubled at 15 mg/kg IV since the proposed administration of the 15-mg/kg dose was b.i.d.
‡ The maximum dose for 20 mg/kg was 1 g.
§ The maximum dose for 40 mg/kg was 2 g.
‖ Adults administered a single 1-g IV dose (Protocol 009).
CI = Confidence interval.
GM = Geometric mean.
GMR = Geometric mean ratio.

Data Source: [2.1; 2.2.1]

Table 4. AUC(0-∞) (µg•hr/mL) for Total Ertapenem Following the Administration of Single IV Doses in Pediatric Patients 3 to 6, 7 to 12, 13 to 23 Months and 2 to 6, 7 to 12, 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g IV])

Ertapenem Dose	Age Group	N	GM	$AUC_{(0-\infty)}$ GMR (Children/Adults)	90% CI
15 mg/kg†	Adults‖	16	568.400	--	
	7 to 12 years	4	610.521	1.074	(0.88, 1.32)
	2 to 6 years	4	419.142	0.737	(0.60, 0.90)
	13 to 23 months	4	599.964	1.056	(0.86, 1.30)
	7 to 12 months	4	585.308	1.030	(0.84, 1.26)
	3 to 6 months	4	423.774	0.746	(0.61, 0.91)
20 mg/kg‡	Adults‖	16	568.400	--	
	13 to 17 years	5	503.884	0.887	(0.70, 1.12)
	7 to 12 years	2	388.189	0.683	(0.49, 0.96)
	2 to 6 years	6	374.605	0.659	(0.53, 0.82)
	13 to 23 months	7	336.245	0.592	(0.48, 0.73)
	7 to 12 months	2	380.393	0.669	(0.48, 0.94)
	3 to 6 months	3	377.848	0.665	(0.50, 0.89)
40 mg/kg§	Adults‖	16	568.400	--	
	13 to 17 years	7	727.456	1.280	(1.05, 1.56)
	7 to 12 years	3	782.338	1.376	(1.05, 1.81)
	2 to 6 years	7	580.868	1.022	(0.84, 1.25)
	13 to 23 months	3	718.157	1.263	(0.96, 1.66)
	7 to 12 months	3	649.980	1.144	(0.87, 1.50)
	3 to 6 months	3	466.863	0.821	(0.62, 1.08)

† The $AUC_{(0-\infty)}$ was doubled at 15 mg/kg IV since the proposed administration of the 15-mg/kg dose was b.i.d.
‡ The maximum dose for 20 mg/kg was 1 g.
§ The maximum dose for 40 mg/kg was 2 g.
‖ Adults administered a single 1-g IV dose (Protocol 009).
CI = Confidence interval.
GM = Geometric mean.
GMR = Geometric mean ratio.

Data Source: [2.1; 2.2.1]

C12 for 20-mg/kg, 40-mg/kg (Tables 5 and 6) and C6 for 15 mg/kg bid (Tables 7 and 8)

- At the 20-mg/kg dose, the GM C12 hr values in children 3 to 23 months and 2 to 12 years of age were generally lower than those observed in young healthy adults receiving a 1-g dose of ertapenem. The C12 hr GMR of children/adults (with corresponding 90% CI) were 0.29 (0.18, 0.47) for 3- to 23-month olds and 0.37 (0.21, 0.65) for 2- to 12-year olds.

- At the 40-mg/kg dose, the GM C12 hr values in children 3 to 23 months and 2 to 12 years of age were also generally lower than those in young healthy adults receiving a 1-g dose of ertapenem. The C12

hr GMR of children/adults (with corresponding 90% CI) were 0.66 (0.46, 0.95) for 3- to 23-month olds and 0.74 (0.49, 1.12) for 2- to 12-year olds.

Table 5. C12 hr (µg/mL) for Total Ertapenem Following the Administration of Single IV Doses in Pediatric Patients 3 to 23 Months, 2 to 12 Years, and 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g IV])

Ertapenem Dose	Age Group	N	GM	$C_{12\ hr}$ GMR (Children/Adults)	90% CI
20 mg/kg†	Adults§	16	8.890	--	
	13 to 17 years	6	6.891	0.775	(0.41, 1.48)
	2 to 12 years	9	3.300	0.371	(0.21, 0.65)
	3 to 23 months	15	2.583	0.291	(0.18, 0.47)
40 mg/kg‡	Adults§	16	8.890	--	
	13 to 17 years	7	11.265	1.267	(0.81, 1.97)
	2 to 12 years	9	6.601	0.743	(0.49, 1.12)
	3 to 23 months	13	5.871	0.660	(0.46, 0.95)

† The maximum dose for 20 mg/kg was 1 g.
‡ The maximum dose for 40 mg/kg was 2 g.
§ Adults administered a single 1-g IV dose (Protocol 009).

Table 6. C12 hr (µg/mL) for Total Ertapenem Following the Administration of Single IV Doses in Pediatric Patients 3 to 6, 7 to 12, 13 to 23 Months and 2 to 6, 7 to 12, 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g IV])

Ertapenem Dose	Age Group	N	GM	$C_{12\ hr}$ GMR (Children/Adults)	90% CI§	95% CI‖
20 mg/kg†	Adults¶	16	8.890	--		
	13 to 17 years	6	6.891	0.775	(0.40, 1.50)	(2.96, 16.1)
	7 to 12 years	3	4.920	0.553	(0.23, 1.31)	(1.49, 16.3)
	2 to 6 years	6	2.703	0.304	(0.16, 0.59)	(1.16, 6.30)
	13 to 23 months	8	2.528	0.284	(0.16, 0.52)	(1.22, 5.26)
	7 to 12 months	3	3.581	0.403	(0.17, 0.96)	(1.08, 11.8)
	3 to 6 months	4	2.110	0.237	(0.11, 0.51)	(0.75, 5.95)
40 mg/kg‡	Adults¶	16	8.890	--		
	13 to 17 years	7	11.265	1.267	(0.83, 1.93)	(6.76, 18.8)
	7 to 12 years	3	10.864	1.222	(0.68, 2.20)	(4.98, 23.7)
	2 to 6 years	6	5.146	0.579	(0.37, 0.90)	(2.96, 8.94)
	13 to 23 months	6	7.965	0.896	(0.57, 1.40)	(4.59, 13.8)
	7 to 12 months	3	5.019	0.565	(0.31, 1.01)	(2.30, 11.0)
	3 to 6 months	4	4.178	0.470	(0.28, 0.79)	(2.12, 8.22)

† The maximum dose for 20 mg/kg was 1 g.
‡ The maximum dose for 40 mg/kg was 2 g.
§ 90% CI for the GMR.
‖ 95% CI for the GM.
¶ Adults administered a single 1-g IV dose (Protocol 009).

The C6 hr (i.e., the midpoint of the intended twice-daily dosing interval) value for total ertapenem following the administration of single 15-mg/kg IV doses to patients 3 to 23 months and 2 to 12 years of age are similar to slightly higher than the concentration of total ertapenem at the midpoint of the dosing interval (C12 hr) following the administration of a single 1-g IV dose of ertapenem in healthy young adults (historical

controls).The C6 hr values are well above the established highest aerobic susceptibility breakpoint as indicated in the product circular (2 µg/mL).

Table 7. C6 hr (µg/mL) of Total Ertapenem in Pediatric Patients 3 to 23 Months and 2 to 12 Years of Age Following Administration of a Single 15-mg/kg Dose Versus C12 hr (µg/mL) in Young Healthy Adult Subjects Following Administration of a Single 1-g Dose of Ertapenem (Control From Protocol 009)

Age Group	N	GM	$C_{6\,hr}$ GMR (Children/Adults)	90% CI
Adults	16	8.890	--	
2 to 12 years	8	10.700	1.204	(0.88, 1.64)
3 to 23 months	12	12.723	1.431	(1.09, 1.88)

CI = Confidence interval.
GM = Geometric mean.
GMR = Geometric mean ratio.

Data Source: [2.1; 2.2.1]

Table 8. C6 hr (µg/mL) for Total Ertapenem Following the Administration of a Single IV 15-mg/kg Dose in Pediatric Patients 3 to 6, 7 to 12, 13 to 23 Months and 2 to 6, and 7 to 12 Years of Age

Age Group	N	$C_{6\,hr}$ GM	95% CI
7 to 12 years	4	14.222	(8.96, 22.6)
2 to 6 years	4	8.050	(5.07, 12.8)
13 to 23 months	4	14.901	(9.38, 23.7)
7 to 12 months	4	15.271	(9.62, 24.2)
3 to 6 months	4	9.050	(5.70, 14.4)

CI = Confidence interval.
GM = Geometric mean.

Data Source: [2.1]

Ceoi for 20-mg/kg, 40-mg/kg and 15 mg/kg bid (Tables 9 and 10)

- At the 20-mg/kg dose, the GM Ceoi values in 3- to 23-month olds and 2- to 12-year olds were slightly lower or generally comparable to those in healthy young adults receiving a 1-g dose. The Ceoi GMR of children/adults (with corresponding 90% CI) was 0.82 (0.73, 0.91) for 3- to 23-month olds and 0.95 (0.83, 1.08) for 2- to 12-year olds.

- At the 40-mg/kg dose, the GMs Ceoi values in 3- to 23-month olds and 2- to 12-year olds were higher than that observed in healthy young adults receiving a 1-g dose. The Ceoi GMR of children/adults (with corresponding 90% CI) was 1.26 (1.05, 1.51) for 3- to 23-month olds and 1.55 (1.28, 1.88) for 2- to 12-year olds.

- At the 15-mg/kg dose, as expected, the GM Ceoi values in 3- to 23-month olds and 2- to 12-year olds were lower as compared to those in healthy young adults receiving a 1-g dose. The Ceoi GMR of children/adults (with corresponding 90% CI) was 0.64 (0.54, 0.77) for 3- to 23-month olds and 0.68 (0.55, 0.83) for 2- to 12-year olds.

Table 9. Ceoi (µg/mL) for Total Ertapenem Following the Administration of Single IV Doses in Pediatric Patients 3 to 23 Months and 2 to 12, and 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g IV])

Ertapenem Dose	Age Group	N	GM	C_{eoi} GMR (Children/Adults)	90% CI
15 mg/kg	Adults§	16	153.384	--	
	2 to 12 years	8	103.905	0.677	(0.55, 0.83)
	3 to 23 months	12	98.522	0.642	(0.54, 0.77)
20 mg/kg†	Adults§	16	153.384	--	
	13 to 17 years	5	165.382	1.078	(0.92, 1.26)
	2 to 12 years	8	145.030	0.946	(0.83, 1.08)
	3 to 23 months	15	125.020	0.815	(0.73, 0.91)
40 mg/kg‡	Adults§	16	153.384	--	
	13 to 17 years	7	205.465	1.340	(1.08, 1.66)
	2 to 12 years	10	237.696	1.550	(1.28, 1.88)
	3 to 23 months	13	193.193	1.260	(1.05, 1.51)

† The maximum dose for 20-mg/kg was 1 g.
‡ The maximum dose for 40-mg/kg was 2 g.
§ Adults administered a single 1-g IV dose (Protocol 009).

Table 10. Ceoi (µg/mL) for Total Ertapenem Following the Administration of Single IV Doses in Pediatric Patients 3 to 6, 7 to 12, 13 to 23 Months and 2 to 6, 7 to 12, 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g IV])

Ertapenem Dose	Age Group	N	GM	C_{eoi} GMR (Children/Adults)	90% CI
15 mg/kg	Adults§	16	153.384	--	
	7 to 12 years	4	121.025	0.789	(0.62, 1.00)
	2 to 6 years	4	89.206	0.582	(0.46, 0.74)
	13 to 23 months	4	122.530	0.799	(0.63, 1.02)
	7 to 12 months	4	101.878	0.664	(0.52, 0.84)
	3 to 6 months	4	76.608	0.499	(0.39, 0.63)
20 mg/kg†	Adults§	16	153.384	--	
	13 to 17 years	5	165.382	1.078	(0.93, 1.26)
	7 to 12 years	2	152.555	0.995	(0.79, 1.24)
	2 to 6 years	6	142.605	0.930	(0.81, 1.07)
	13 to 23 months	8	114.297	0.745	(0.65, 0.85)
	7 to 12 months	3	147.904	0.964	(0.80, 1.16)
	3 to 6 months	4	131.862	0.860	(0.73, 1.02)
40 mg/kg‡	Adults§	16	153.384	--	
	13 to 17 years	7	205.465	1.340	(1.08, 1.67)
	7 to 12 years	3	235.757	1.537	(1.14, 2.08)
	2 to 6 years	7	238.532	1.555	(1.25, 1.93)
	13 to 23 months	5	194.431	1.268	(0.99, 1.62)
	7 to 12 months	4	226.952	1.480	(1.13, 1.94)
	3 to 6 months	4	163.148	1.064	(0.81, 1.39)

† The maximum dose for 20-mg/kg was 1 g.
‡ The maximum dose for 40-mg/kg was 2 g.
§ Adults administered a single 1-g IV dose (Protocol 009).

Plasma Clearance following 15 mg/kg, 20-mg/kg, and 40-mg/kg (Table 11 and 12)
The plasma clearance GM values of ertapenem, on a per kg basis following 15-mg/kg or 20-mg/kg doses in children 3 to 23 months and 2 to 12 years of age were approximately 2-fold higher, as compared to those following a 1-g dose administered to healthy young adults. At 15 mg/kg, the CLp GMR of children/adults (with corresponding 90% CI) were 2.2 (1.86, 2.61) and 2.3 (1.90, 2.80) for children 3 to 23 months and 2 to 12 years, respectively. At 20 mg/kg, the CLp GMR of children/adults (with corresponding 90% CI) were 2.2 (1.84, 2.63) and 2.0 (1.68, 2.52) for children 3 to 23 months and 2 to 12 years, respectively. Following a dose

of 40 mg/kg administered to children 3 to 23 months and 2 to 12 years of age, plasma clearance GMs was approximately 2.5 times higher than that observed in healthy young adults receiving a 1-g dose. The CLp GMR of children/adults (with corresponding 90% CI) were 2.5 (2.07, 3.11) and 2.4 (2.0, 3.0) for children 3 to 23 months and 2 to 12 years, respectively.

Table 11. CLp (mL/min/kg) for Total Ertapenem Following the Administration of Single IV Doses in Pediatric Patients 3 to 23 Months and 2 to 12, and 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g IV])

Ertapenem Dose	Age Group	N	GM	CL_p GMR (Children/Adults)	90% CI
15 mg/kg	Adults[§]	16	0.429	–	
	2 to 12 years	8	0.988	2.306	(1.90, 2.80)
	3 to 23 months	12	0.944	2.201	(1.86, 2.61)
20 mg/kg[†]	Adults[§]	16	0.429	--	
	13 to 17 years	5	0.601	1.402	(1.10, 1.78)
	2 to 12 years	8	0.882	2.058	(1.68, 2.52)
	3 to 23 months	12	0.943	2.201	(1.84, 2.63)
40 mg/kg[‡]	Adults[§]	16	0.429	--	
	13 to 17 years	7	0.770	1.796	(1.43, 2.26)
	2 to 12 years	10	1.050	2.449	(2.00, 3.00)
	3 to 23 months	9	1.086	2.534	(2.07, 3.11)

[†] The maximum dose for 20-mg/kg was 1 g.
[‡] The maximum dose for 40-mg/kg was 2 g.
[§] Adults administered a single 1-g IV dose (Protocol 009).

Table 12. CLp (mL/min/kg) for Total Ertapenem Following the Administration of Single IV Doses in Pediatric Patients 3 to 6, 7 to 12, 13 to 23 Months and 2 to 6, 7 to 12, 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g IV])

Ertapenem Dose	Age Group	N	GM	CL_p GMR (Children/Adults)	90% CI
15 mg/kg	Adults[§]	16	0.429	–	
	7 to 12 years	4	0.819	1.911	(1.52, 2.40)
	2 to -6 years	4	1.193	2.783	(2.22, 3.50)
	13 to 23 months	4	0.833	1.944	(1.55, 2.44)
	7 to 12 months	4	0.854	1.993	(1.59, 2.50)
	3 to 6 months	4	1.180	2.753	(2.19, 3.46)
20 mg/kg[†]	Adults[§]	16	0.429	–	
	13 to 17 years	5	0.601	1.402	(1.09, 1.80)
	7 to 12 years	2	0.859	2.003	(1.39, 2.88)
	2 to 6 years	6	0.890	2.076	(1.65, 2.62)
	13 to 23 months	7	0.991	2.313	(1.86, 2.88)
	7 to 12 months	2	0.876	2.044	(1.42, 2.94)
	3 to 6 months	3	0.882	2.058	(1.52, 2.79)
40 mg/kg[‡]	Adults[§]	16	0.429	–	
	13 to 17 years	7	0.770	1.796	(1.44, 2.24)
	7 to 12 years	3	0.852	1.988	(1.46, 2.70)
	2 to 6 years	7	1.148	2.678	(2.15, 3.34)
	13 to 23 months	3	0.923	2.154	(1.64, 2.83)
	7 to 12 months	3	1.026	2.393	(1.76, 3.25)
	3 to 6 months	3	1.428	3.331	(2.45, 4.52)

[†] The 20-mg/kg was 1 g.
[‡] The 40-mg/kg was 2 g.
[§] Adults administered 1 g from Protocol 009.

Half-Life (t1/2) (Table 12):

The half-life (t½) for total ertapenem at the 15-, 20-, and 40-mg/kg dose levels for patients 3 months to 17 years of age is given in Tables 12 and 13. The harmonic mean t½ in 13- to 17-year-old patients was comparable to that observed in healthy young subjects. Mean t½ was lower in 3- to 23-month- and 2- to 12-year-old patients than that observed in adolescents or young healthy adults.

Table 12. Harmonic Mean (Pseudo SD) Half-Life (hours) of Total Ertapenem Following the Administration of Single IV Doses in Pediatric Patients 3 to 23 Months, 2 to 12, and 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g and 2 g IV])

Age Group	Ertapenem Dose		
	15 mg/kg	20 mg/kg	40 mg/kg
3 to 23 months	2.5 (1.1)	2.9 (1.0)	2.7 (0.5)
2 to 12 years	2.4 (1.0)	2.8 (1.3)	2.9 (0.5)
13 to 17 years	--	4.0 (0.8)	3.7 (0.7)
Adults	--	3.8 (0.5)†	3.8 (0.5)‡

† Half-life following administration of a single 1-g dose.
‡ Half-life following administration of a single 2-g dose.
SD = Standard deviation.

Data Source: [2.1; 2.2.1]

Volume of Distribution (Vss)

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

Urinary Excretion (Fe) and Renal Clearance (CLR) (Table 13):

The mean (SD) Fe (% of dose excreted in urine) and the CLR (renal clearance on per kg basis) of total ertapenem following single IV doses in pediatric patients 2 to 6 years, 7 to 12 years, and 13 to 17 years of age are given in Table 9. Note that these data are based on small numbers of patients in each group. The mean Fe are based on even a smaller number of patients because the urine collection was incomplete. For the purpose of comparison, the mean (SD) Fe and CLR values in healthy adults following 1-g or 2-g doses from Protocol 009 are also included. The Fe of ertapenem in pediatric patients appears to be generally comparable to that observed in healthy adult subjects. The CLR was observed to be approximately 2-fold higher in 2- to 12-year-old patients and approximately 1.5-fold higher in 13- to 17-year-old patients as compared to the observed values in healthy adult subjects.

The values for <2-year-old patients are variable and quite low for a few of the patients (10 to 14% of dose recovered in urine).

Table 13. Mean (SD) Fe and CLR of Ertapenem Following Single IV Doses in Pediatric Patients 2 to 6, 7 to 12, and 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g and 2 g IV])

Age Group	N	$F_{e\ (0\text{-}24\ hr)}$ (%)	N	CL_R (mL/min/kg)
2 to 6 Years	3	58 (7)	7	0.48 (0.19)
7 to 12 Years	6	56 (17)	7	0.48 (0.16)
13 to 17 Years	7	47 (6)	8	0.31 (0.10)
Adults	16	44 (14)	16	0.21 (0.09)

Data Source: [2.1; 2.2.1]

Pharmacokinetics of Unbound Ertapenem (Table 14)

The mean (SD) pharmacokinetic parameters for plasma unbound ertapenem following the administration of single doses of 20-mg/kg and 40-mg/kg dose is given in Table 15. The mean and (SD) values are based on a small number of patients in each age group and, therefore, must be interpreted with caution. Although not measured here due to restrictions in blood sampling, both Ceoi and C12hr of unbound ertapenem following a 15-mg/kg dose in the less than 13-year-old patients would be expected to be somewhat lower than the values reported here following the 20-mg/kg dose. The AUC(0-∞) of unbound ertapenem appeared similar in patients 13 to 17 years of age at the 20-mg/kg dose as compared to healthy young adults receiving a single 1-g dose of ertapenem (36.2 µg•hr/mL in 13- to 17-year olds versus 33.2 µg•hr/mL in adults). C12hr also appeared similar (0.37 µg/mL in 13- to 17-year olds versus 0.41 µg/mL in adults). The Ceoi was 19.9 µg/mL in 13- to 17-year olds versus 12.9 µg/mL in adults receiving a 1-g dose. This is consistent with a slightly higher fraction unbound at the end of infusion (Fueoi) in 13- to 17-year olds as compared to adults (0.12 versus 0.08).

Table 15. Mean (SD) Pharmacokinetic Parameters of Unbound Ertapenem Following Single IV Doses in Pediatric Patients 3 to 23 Months, 2 to 6, 7 to 12, and 13 to 17 Years of Age (Control From Protocol 009 Healthy Adults [1 g and 2 g IV])

Age Group/ (N)	Dose (mg/kg)	Dose-Adjusted C_{eoi} (µg/mL)	Dose-Adjusted C_{1hr} (µg/mL)	Dose-Adjusted C_{12hr} (µg/mL)	Fu_{eoi}	Fu_{1hr}	Fu_{12hr}	Dose-Adjusted AUC (µg•hr/mL)	CL_p (mL/min/kg)
3 to 23 months									
(2 to 5)	20	15.4 (2.6)	NA	0.28 (0.38)	0.12 (0.03)	NA	0.10 (0.02)	NA	NA
(6)	40	33.0 (10.8)	NA	0.50 (0.31)	0.17 (0.06)	NA	0.05 (0.02)	NA	NA
2 to 6 years									
(2 to 5)	20	17.7 (5.1)	9.4 (2.4)	0.21 (0.31)	0.13 (0.06)	0.10 (0.04)	0.05 (0.01)	NA	NA
(1 to 3)	40	44.9 (15.0)	18.2 (NA)	0.21 (NA)	0.19 (0.06)	0.14 (NA)	0.05 (NA)	NA	NA
7 to 12 years									
(2 to 3)	20	14.2 (2.6)	7.9 (0.04)	0.65 (0.49)	0.09 (0.02)	0.08 (0.01)	0.10 (0.08)	29.0 (2.8)	11.6 (1.1)
(2 to 3)	40	42.7 (2.0)	21.1 (4.7)	0.55 (0.09)	0.17 (0.02)	0.12 (0.02)	0.05 (0.00)	72.5 (11.6)	9.3 (1.5)
13 to 17 years									
(1 to 4)	20	19.9 (5.1)	11.1 (NA)	0.37 (0.10)	0.12 (0.02)	0.10 (NA)	0.05 (0.01)	36.2 (8.0)	9.4 (2.1)
(5 to 6)	40	61.5 (25.4)	27.3 (11.5)	0.84 (0.58)	0.23 (0.07)	0.14 (0.03)	0.06 (0.02)	98.8 (43.9)	5.9 (1.3)
Adults									
(16)	1 g	12.9 (3.2)	7.8 (1.9)	0.41 (0.16)	0.08 (0.01)	0.07 (0.01)	0.04 (0.01)	33.2 (5.5)	7.5 (1.4)
(16)	2 g	43.3 (14.8)	20.8 (5.7)	0.73 (0.20)	0.15 (0.04)	0.10 (0.02)	0.04 (0.01)	76.6 (13.2)	6.5 (1.0)

The mean (SD) values for pediatric groups, especially for the younger ones, must be interpreted with caution since they are based on very small numbers of patients.
AUC = $AUC_{(0-\infty)}$
NA = Not available.
Values <LOQ were set to zero.

Brief Summary of Clinical Adverse Experiences

Most of the adverse experiences that were observed were not considered to be drug related and were most likely related to the baseline condition that led to hospitalization of the patient. There were 12 serious adverse experiences, of which, only one ("overdose" to study drug) was considered to be definitely drug related. Of the 58 non-serious clinical adverse experiences, 55 were considered to be either probably not (14 adverse experiences) or definitely not (41 adverse experiences) drug related by the investigator. Two episodes of nausea and 1 episode of injection site infiltration were considered to be possibly drug related. No other drug-related adverse experiences were reported by the investigator. No patient discontinued from the study due to a serious or non-serious clinical adverse experience.

4.2.2. Study Protocol 038. A Prospective, Multicenter, Randomized, Open-Label, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of Ertapenem Sodium (MK-0826) Versus Ticarcillin/Clavulanate in the Treatment of Complicated Intra-abdominal Infections and Acute Pelvic Infections in Pediatric Patients.

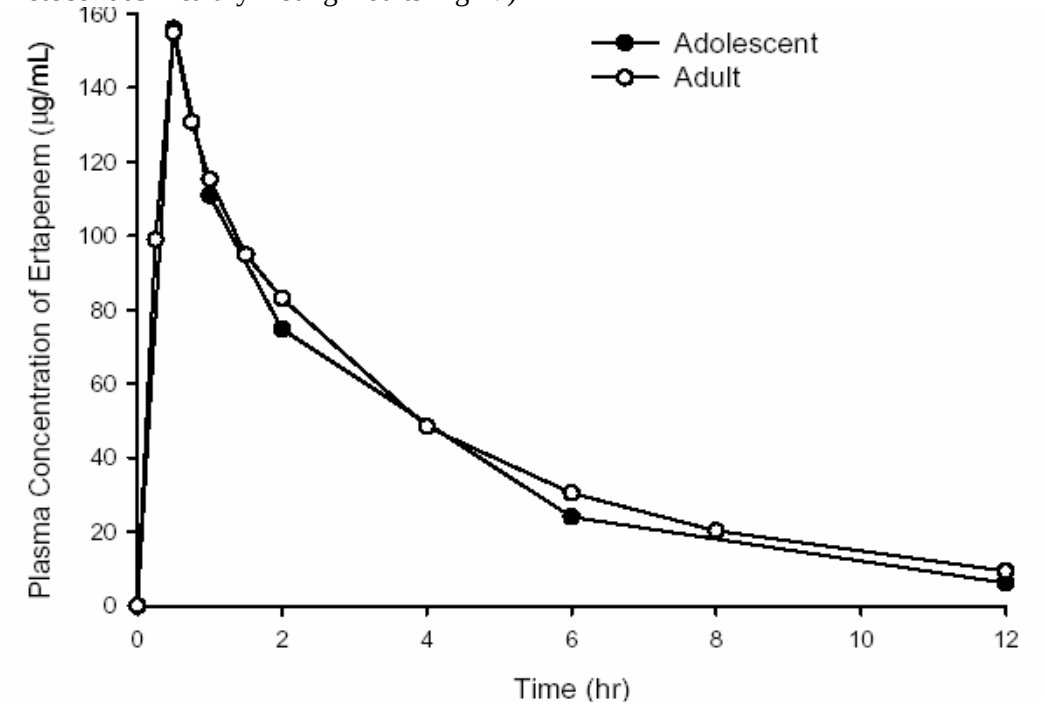
Investigators/Study Centers: Multicenter: Fifteen (15) centers participated in this study (12 centers in the United States and 3 internationally).

Primary Therapy Period: 27-Mar-2002 through 17-Jan-2004.

This was a Phase IIb safety and efficacy study, in which a pharmacokinetic sub-study was conducted. The study was open to enrollment of pediatric patients 3 months to 17 years of age, however patients 2 to 17 years of age were actually enrolled. This age distribution accurately reflects the age ranges for the infectious diseases under study in children: complicated appendicitis and acute obstetric-related pelvic infections in adolescent females. The ertapenem dosing regimens utilized in the study (15 mg/kg b.i.d. for children 3 months to 12 years of age and 1 g once daily for 13 to 17 year olds) were based on results from an ertapenem single dose PK pediatric study (Protocol 028) where they approximated key pharmacokinetic parameters for the 1 g once daily licensed regimen in adults: Cmax, total AUC exposure over 24 hours and time above MIC (T>MIC) for anticipated pathogens.

At selected study sites, plasma samples were obtained from 3 patients, aged 13 to 17 years, that received 1-g IV doses of ertapenem infused over 30 minutes and 1 that received ceftriaxone. The mean plasma concentration profile of ertapenem in 13- to 17-year-old patients is shown in the figure provided below (Figure 3). The mean ertapenem concentration time profiles for the adolescent patients were similar to young healthy subjects (historical controls from Protocol 009).

Figure 4. Mean (N=3) Plasma Concentration Profile of Ertapenem in 13- to 17-Year-Old Patients Following the Administration of a Single 1-g IV Dose Infused Over 30 Minutes, Protocol 036 (Historical Control From Protocol 009 Healthy Young Adults 1-g IV)



The mean plasma concentration of ertapenem in adolescent patients were 155.9 ug/mL , at 0.5 hours (end of infusion), 110.9 ug/mL at 1 hours postdose, 74.8 ug/mL at 2 hours postdose, 24.0 µg/mL at 6 hours postdose, and 6.2 µg/mL at 12 hours postdose. The individual plasma ertapenem pharmacokinetic parameter values for the 3 patients who received ertapenem are provided in the Table 16 below. The Ceoi ranged from 144 to 162 µg/mL which was similar to healthy young adults receiving 1-g dose in Protocol 009 which ranged from 115 to 199 µg/mL with a mean of 155 µg/mL The C12 hr value was 4.4 µg/mL in 1 adolescent and 7.9 µg/mL in the other. One patient had a C12 hr sample obtained 15 minutes after infusion and therefore was not evaluable. The C12 hr value in healthy young adults ranged from ~3.5 to 14.5 µg/mL with a mean of 9.3 µg/mL. Thus, the values in the 2 other adolescents were within the range of values seen in healthy young adults. Moreover, the values for both adolescent patients exceeded the established susceptibility breakpoints as indicated in the product circular. The plasma clearance (CLp) in healthy young adults receiving 1-g dose ranged from 23.9 to 35.0 mL/min with a mean of 29.5 mL/min. The CLp value for 1 of the 2 adolescents (31.1 mL/min) was within this range and for the other (41.6 mL/min) was slightly outside. The Vdss values of 7.6 and 7.9L in the 2 adolescents were close to the mean Vdss value of ~8L in healthy young adults receiving the 1-g dose. While the pharmacokinetic parameters for patient AN 2037 could not be assessed except for Ceoi, it is worth noting that the plasma concentrations of ertapenem in AN 2037 at 1, 2, and 6 hour (113.4, 74.6, and 24.7 µg/mL, respectively) were all between those of AN 1216 and AN 2013 (Table 15) below:

Table 15. Individual Pharmacokinetic Parameters of Ertapenem in 13- to 17-Year-Old Patients Following 1-g Once Daily Dose Infused Over 30 Minutes

AN	$AUC_{0-\infty}$ µg•hr/mL_y	C_{eoi} (µg/mL)	$C_{12\,hr}$ (µg/mL)	CL_P (mL/min)	Vd_{ss} (L)
2013	536.3	162.3	7.9	31.1	7.6
2037	NA	160.9	139.4†	NA	NA
1216	400.9	144.6	4.4	41.6	7.9

† Sample was taken 15 minutes after the start of the second dose of ertapenem and thus was not evaluable for this parameter.
NA = Not available.

4.2.3. Study Protocol 031/032: An Open-Label, Multicenter Study to Evaluate the Cerebral Spinal Fluid Concentration Profile of MK-0826 After Intravenous Administration in Pediatric Patients With Meningitis.

The primary objective of the study was to assess the pharmacokinetics of ertapenem in cerebral spinal fluid in pediatric patients with meningitis.

This study was a multi-center, open-label, single intravenous dose study in clinically stable children and adolescents aged ≥3 months to ≤17 yrs who were receiving intravenous cefotaxime (200 mg/kg IV q8h) or other antibiotic therapy for bacterial meningitis. A single intravenous 15 mg/kg or 20 mg/kg dose of ertapenem (maximum 1 gram) was infused over 30 min as close as possible to the dosing interval midpoint for each patient's ongoing cefotaxime or other appropriate antibiotic therapy. Ertapenem was administered on day 2 or 3 of therapy for meningitis. This study was conducted both in the US (protocol 031) and outside the US (protocol 032).

This study report was reviewed by Dr. Charles Bonapace as part of the Written Request IND 48,485 (S-471) submission dated Nov 07, 2003. The report of this study is summarized below:

Of the 13 patients entered in the study, 11 were considered evaluable (i.e. received ertapenem and had CSF samples collected for ertapenem concentration determination). The concentration of ertapenem at the end of infusion (0.5 hrs) and from corresponding plasma and CSF samples obtained at 2, 4, 6, and 12 hrs are shown in Figure 1. The mean (SD) plasma ertapenem concentration at the end of infusion was 145.9 (49.5) µg/mL for the 20 mg/kg cohort and 82.7 (19.8) µg/mL for the 15 mg/kg cohort. The median CSF concentrations were 0.53 µg/mL and 0.70 µg/mL for the 15 mg/kg and 20 mg/kg cohorts, respectively. Except for two patients in which the CSF concentration exceeded 1 µg/mL (5.12 µg/mL at 4.67 hrs and 1.69 µg/mL at 12.75 hrs, both in the 20 mg/kg cohort), the CSF concentrations of ertapenem did not exceed 1 µg/mL. The individual CSF/plasma ratios ranged from 0.01 to 0.22 following administration of 20 mg/kg and 0.02 to 0.07 following administration of 15 mg/kg.

Based on the low concentration of ertapenem in CSF observed in the above study, the Agency concurred with the Sponsor's request to remove the requirement to conduct a clinical efficacy study in pediatric patients with bacterial meningitis.

4.3. Cover Sheet and OCPB filing/Reviewing Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA Number	21-337	Brand Name	INVANZ™
OCPB Division	DPE III, HFD 880	Generic Name	Ertapenem Sodium
Medical Division	ODE IV, HFD 520	Drug Class	Antiinfective
OCPB Reviewer	Chandra S. Chaurasia, Ph. D.	Indication(s)	Treatment of moderate to severe infections caused by susceptible strains of designated microorganisms
OCPB Team Leader	Venkateswar Jarugula, Ph. D.	Dosage Form	Injection
Type of Application	NDA	Sponsor	Merck & Co. Inc., Rahway, NJ
Type of Submission	Efficacy Supplement Pediatric Written Request	Strength	1 gm
Related NDAs/ANDAs/INDs	NDA 21-337 IND 48,485	Route of Administration	Intravenous/Intramuscular Injection
Date of Submission	Nov 19, 2004	Dosing Regimen	In patients 13 years or older: One gram given once a day In patients 3 months to 12 years: 15 mg/kg bid (not to exceed 1 g/day).
Estimated Due Date of OCPB Review	March 25, 2005	Document Submission Format	Paper and Electronic
PDUFA Due Date	May 25, 2005	Priority Classification	Priority Approval (PA)
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	***X***			
Labeling	**X**			

Reference Bioanalytical and Analytical Methods	**X**			Plasma samples collected were analyzed for total and unbound ertapenem and the urine samples collected were analyzed for total ertapenem (b) (4) using HPLC/UV method. The LLOQs were 0.125 mcg/mL for plasma unbound, and 0.25 mcg/mL for plasma bound and urine total drug assays.
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose in **pediatric population**:				
multiple dose:				

Patients-				
single dose:	**X**	**2**		**Protocol No. 028: Multicenter Phase 1,** An open, intravenous study to evaluate the plasma concentration profiles of MK-0826 in patients aged 3 months through 17 years. (N=84: 3-24 months – 24 M; 4-24 months - 19 F; 4-11 years – 10M; 2-12 years 18 F; 13-16 years – 8M; and 14-15 years – 5F) Single IV dose of 15, 20, or 40-mg/kg infused over 30 min. Blood samples assayed for total and unbound ertapenem for determination of PK parameters C6hr, C12hr, Ceoi, $AUC_{0-\infty}$, CL, $t_{1/2}$. Urinary samples were collected up to 24 hr post-dose. **Protocol No. 031C1: Multicenter Phase 1,** An open, intravenous study to evaluate the cerebrospinal fluid concentration profiles of MK-0826 in patients aged 3 months through 17 years. A single dose (15 mg/kg or 20 mg/kg) based on body weight was infused over 30 min to patients 3 months to 13 years (8M and 5F). Based on variable and low CSF drug levels, this study was terminated early with concurrence by FDA.

multiple dose:	**X**	**1**		**Protocol No. 036/ Multicenter Phase IIb.** A Prospective, multicenter, double-blind, randomized, comparative study to evaluate the safety, local tolerability, and clinical outcome of etrapenem sodium (MK-0826) versus ceftriaxone sodium in pediatric patients with complicated urinary tract infection, skin and soft tissue infection, or community-acquired pneumonia**.** In essence PK was done on single dose in that blood samples were collected from 4 patients 13-17 years of age at selected study sites prior to first dose of study drug on Day 1 and at 30 min, 1, 2, 6, and 12 hours after the start of the infusion of the first dose. Note: In all 400 patients 3 months through 17 years were included in the clinical trial. For children 3 months to 12 years of age, ertapenem was given bid as 15 mg/kg parenteral dose to a maximum of 1 g. Children 13 years of age or older received ertapenem 1 g as a single daily dose.
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:	***X***			Pooled Data
pediatrics:	**X**			
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution: In Vitro				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		
Filability and QBR comments				

	"X" if yes	Comments
Application filable?	***YES***	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	From Clinical Pharmacology and Biopharmaceutics perspective Has the Sponsor addressed questions per Agency's Written Request (WR)? Is the necessary information provided in the proposed labeling based on the PK studies undertaken per WR?	
Other comments or information not included above		
Primary reviewer Signature and Date	Chandra S. Chaurasia, Ph. D.	
Secondary reviewer Signature and Date	Venkateswar Jarugula, Ph. D.	

Chandra S. Chaurasia, Ph.D. _____ Date: _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Venkateswar Jarugula, Ph. D.. _____ Date: _____
Team Leader
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CC: NDA 21-337, HFD-520 (S. Samanta), HFD-880 (J. Lazor, A. Selen, V. Jarugula, C. Chaurasia)

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/s/

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