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 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
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Venkateswar Jarugula, Ph.D. _____Date: _____
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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)

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/s/

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