

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID#: D050100

DATE: May 24, 2006

TO: Lisa Mathis, M.D., Director
Division of Pediatric Drug Development
and
M. Dianne Murphy, M.D., Director
Office of Pediatric Therapeutics (OPT), OC

FROM: Ronald Wassel, Pharm.D., Postmarketing Safety Evaluator
Division of Drug Risk Evaluation

THROUGH: Rosemary Johann-Liang, M.D., Deputy Director
for
Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation

SUBJECT: 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Ertapenem (Invanz[®])
Pediatric Exclusivity Approval Date: February 11, 2005

1. Executive Summary

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of ertapenem in pediatric patients. Up to the "data lock" date of 3/11/2006, AERS contained 357 cases for ertapenem (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 0.6 % of the total (2/357).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, 2/11/2005 to 2/11/2006. We used an AERS data lock date of 3/11/2006, to allow time for reports received up to 2/11/2006, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 99 cases (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent 0% of the total number of cases (0/99). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

This review does not reveal any new safety concerns for the use of ertapenem in pediatric patients. We will continue routine monitoring of adverse events in pediatric patients.

2. Products, Indications, Pediatric Labeling, and Pediatric Filing History

Products:

NDA 21-337 Injectable; IM, IV (infusion) EQ 1 gm base/vial Approved 11/21/2001

Indications:

INVANZ is indicated for the treatment of patients with the following moderate to severe infections caused by susceptible isolates of the designated microorganisms:

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

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

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

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

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

Pediatric labeling:

Under PRECAUTIONS/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:

- 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.

Under ADVERSE REACTIONS/Pediatric patients—

Clinical studies enrolled 384 patients treated with ertapenem; in some of the clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial. (See CLINICAL STUDIES.) The overall adverse experience profile in pediatric patients is comparable to that in adult patients. Table 7 shows the incidence of adverse experiences reported in $\geq 1.0\%$ of pediatric patients in clinical studies. The most common drug-related adverse experiences in pediatric patients treated with INVANZ, including those who were switched to therapy with an oral antimicrobial, were diarrhea (6.5%), infusion site pain (5.5%), infusion site erythema (2.6%), vomiting (2.1%).

Table 7 Incidence (%) of Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ³1.0% of Pediatric Patients Treated With INVANZ in Clinical Studies			
Adverse Events	INVANZ* [†] (N=384)	Ceftriaxone* (N=100)	Ticarcillin/ Clavulanate [†] (N=24)
Local:			
Infusion Site Erythema	3.9	3	8.3
Infusion Site Induration	1	1	0
Infusion Site Pain	7	4	20.8
Infusion Site Phlebitis	1.8	3	0
Infusion Site Swelling	1.8	1	4.2
Infusion Site Warmth	1.3	1	4.2
Systemic:			
Abdominal Pain	4.7	3	4.2
Upper Abdominal Pain	1	2	0
Constipation	2.3	0	0
Diarrhea	11.7	17	4.2
Loose Stools	2.1	0	0
Nausea	1.6	0	0
Vomiting	10.2	11	8.3
Pyrexia	4.9	6	8.3
Abdominal Abscess	1	0	4.2
Herpes Simplex	1	1	4.2

Nasopharyngitis	1.6	6	0
Upper Respiratory Tract Infection	2.3	3	0
Viral Pharyngitis	1	0	0
Hypothermia	1.6	1	0
Dizziness	1.6	0	0
Headache	4.4	4	0
Cough	4.4	3	0
Wheezing	1	0	0
Dermatitis	1	1	0
Pruritus	1.6	0	0
Diaper Dermatitis	4.7	4	0
Rash	2.9	2	8.3
<p>* Includes Phase IIb Complicated skin and skin structure infections, Community acquired pneumonia and Complicated urinary tract infections studies in which patients 3 months to 12 years of age received INVANZ 15 mg/kg IV twice daily up to a maximum of 1 g or ceftriaxone 50 mg/kg/day IV in two divided doses up to a maximum of 2 g, and patients 13 to 17 years of age received INVANZ 1 g IV daily or ceftriaxone 50 mg/kg/day IV in a single daily dose.</p> <p>† Includes Phase IIb Acute pelvic infections and Complicated intra-abdominal infections studies in which patients 3 months to 12 years of age received INVANZ 15 mg/kg IV twice daily up to a maximum of 1 g and patients 13 to 17 years of age received INVANZ 1 g IV daily or ticarcillin/clavulanate 50 mg/kg for patients <60 kg or ticarcillin/clavulanate 3.0 g for patients >60 kg, 4 or 6 times a day.</p>			

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

General Disorders and Administration Site Condition: chest pain, infusion site pruritus;

Infections and Infestations: candidiasis, ear infection, oral candidiasis;

Metabolism and Nutrition Disorders: decreased appetite;

Musculoskeletal and Connective Tissue Disorders: arthralgia;

Nervous System Disorders: somnolence;

Psychiatric Disorders: insomnia;

Reproductive System and Breast Disorders: genital rash;

Respiratory, Thoracic and Mediastinal Disorders: pleural effusion, rhinitis, rhinorrhea;

Skin and Subcutaneous Tissue Disorders: dermatitis atopic, rash erythematous, skin lesion;

Vascular Disorders: phlebitis.

Under ADVERSE REACTIONS/Adverse Laboratory Changes/Pediatric patients—

Laboratory adverse experiences that were reported during therapy in $\geq 1.0\%$ of pediatric patients treated with INVANZ in clinical studies are presented in Table 9. Drug-related laboratory adverse experiences that were reported during therapy

in $\geq 2.0\%$ of pediatric patients treated with INVANZ, including those who were switched to therapy with an oral antimicrobial, in clinical studies were neutrophil count decreased (3.0%), ALT increased (2.2%), and AST increased (2.1%).

Table 9 Incidence* (%) of Specific Laboratory Adverse Experiences Reported During Study Therapy Plus 14- Day Follow-Up in $\geq 1.0\%$ of Pediatric Patients Treated With INVANZ in Clinical Studies			
Adverse laboratory experiences	INVANZ (n [†] =379)	Ceftriaxone (n [†] =97)	Ticarcillin/Clavulanate (n [†] =24)
ALT Increased	3.8	1.1	4.3
Alkaline Phosphatase Increased	1.1	0	0
AST Increased	3.8	1.1	4.3
Eosinophil Count Increased	1.1	2.1	0
Neutrophil Count Decreased	5.8	3.1	0
Platelet Count Increased	1.3	0	8.7
* Number of patients with laboratory adverse experiences/Number of patients with the laboratory test; where at least 300 patients had the test † Number of patients with one or more laboratory tests			

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

Under OVERDOSAGE—

In pediatric clinical studies, a single IV dose of 40 mg/kg up to a maximum of 2 g did not result in toxicity.

Under CLINICAL STUDIES/Pediatric patients—

Ertapenem was evaluated in pediatric patients 3 months to 17 years of age in two randomized, multicenter clinical trials. The first study enrolled 404 patients and compared ertapenem (15 mg/kg IV every 12 hours in patients 3 months to 12 years of age, and 1 g IV once a day in patients 13 to 17 years of age) to ceftriaxone (50 mg/kg/day IV in two divided doses in patients 3 months to 12 years of age and 50 mg/kg/day IV as a single daily dose in patients 13 to 17 years of age) for the treatment of complicated urinary tract infection (UTI), skin and soft tissue infection (SSTI), or community-acquired pneumonia (CAP). Both regimens allowed the option to switch to oral amoxicillin/clavulanate for a total of up to 14 days of treatment (parenteral and oral). The microbiological success rates

in the evaluable per protocol (EPP) analysis in patients treated for UTI were 87.0% (40/46) for ertapenem and 90.0% (18/20) for ceftriaxone. The clinical success rates in the EPP analysis in patients treated for SSTI were 95.5% (64/67) for ertapenem and 100% (26/26) for ceftriaxone, and in patients treated for CAP were 96.1% (74/77) for ertapenem and 96.4% (27/28) for ceftriaxone.

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

Pediatric Filing History:

The original Pediatric Written Request (WR) was issued on 5/15/2000 and amended twice, on 4/12/2002 and 4/28/2004. The pediatric efficacy supplement was approved on 5/18/2005 and pediatric exclusivity was granted on 2/11/2005.

3. AERS Search Results: Ertapenem

3.1 Count of Reports: AERS Search including all sources – U.S. & foreign from marketing approval date (Table 1)

Table 1: Crude counts¹ of AERS Reports for All Sources from Marketing Approval Date (11/21/2001) through 3/11/2006 (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	222 (176)	172 (127)	23 (9)
Pediatrics (0-16 yrs.)	2 (2)	1 (1)	0 (0)
Age unknown (Null values)	133 (119)	73 (64)	8 (4)
Total	357 (297)	246 (192)	31 (13)

¹ May include duplicates
² Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)

Table 2: Crude counts¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (2/11/2005) through 3/11/2006 (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	71 (49)	64 (43)	10 (3)
Pediatrics (0-16 yrs)	0 (0)	0 (0)	0 (0)
Age unknown (Null Values)	28 (26)	28 (26)	2 (2)
Total	99 (75)	92 (69)	12 (5)
¹ May include duplicates			
² Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.			

4. Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity.

There were no pediatric adverse event reports received during the 1-year post-pediatric exclusivity period.

Regarding the two cases that were received previously, one case involved a generalized rash in a 13-year-old female, and the other case turned out not to have been related to ertapenem (neurologic changes as the result of an abscess in the frontal area of the brain).

5. Summary/Recommendations

There were no reports of adverse events related to ertapenem in the one-year pediatric exclusivity period and there are no deaths related to ertapenem in pediatric patients in AERS. Of the two reports for ertapenem in pediatric patients, only one was causally related, which involved a generalized rash.

This review does not reveal any new safety concerns for the use of ertapenem in pediatric patients. We will continue routine monitoring of adverse events in pediatric patients.

Ronald Wassel, Pharm.D.
Safety Evaluator

Concur:

Melissa Truffa, R.Ph.
Team Leader

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

/s/

Ronald Wassel
5/24/2006 02:27:35 PM
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
5/25/2006 05:27:48 PM
MEDICAL OFFICER