EXECUTIVE SUMMARY

Division of Anti-Infective and Ophthalmology Products

Summary of Clinical Review of Studies Submitted in Response to a Pediatric Written Request

Application: 021-337/SE1

Applicant: Merck & Co, Inc.
RY 32-605
P.O. Box 2000
Rathway, N.J. 07065

Drug Name Established: Ertapenem sodium

Proprietary: Invanz™

Route: Intravenous/Intramuscular Injection

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1 Executive Summary

1.1 Recommendation on Regulatory Action

The applicant has submitted a response to a final amended Pediatric Written Request from May 4, 2004 to provide information on the use of ertapenem in pediatric patients. Ertapenem is currently approved for adults at a dose of 1 g once a day for treatment of complicated urinary tract infection (UTI) including pyelonephritis, complicated skin and soft tissue infection (SSSI), community-acquired pneumonia (CAP), complicated intra-abdominal infection (IAI) and acute pelvic infection (API).

The overall safety profile for ertapenem in the pediatric studies submitted is similar to that of the comparators, ceftriaxone and ticarcillin/clavulanate, and is similar to the profile described in the current ertapenem labeling for adults. The most frequently reported drug-related adverse events in patients receiving ertapenem were diarrhea and infusion site pain.

The efficacy findings from this submission, together with safety and pharmacokinetic data presented and the previous demonstration of efficacy of ertapenem in adult patients support the use of ertapenem for the approved indications in pediatric patients 3 months to 17 years of age. The appropriate dosing regimen of ertapenem is 15 mg/kg BID for pediatric patients 3 months to 12 years of age and 1 g once daily for patients 13 to 17 years of age.

Pediatric Exclusivity was granted by the Agency on February 11, 2005.

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

1.2 Recommendation on Postmarketing Actions

Ertapenem was approved in the United States in 2001 for the same indications in adults, and no changes in current postmarketing requirements are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Ertapenem is a broad-spectrum carbapenem antimicrobial for intravenous/intramuscular administration approved in the United States for use as single-agent therapy in adults for the treatment of community-acquired pneumonia, complicated urinary tract infections, complicated skin and skin structure infections, complicated intra-abdominal infections and acute pelvic infections. This application contains information on the pharmacokinetics, safety and efficacy of ertapenem in the treatment of serious infections in pediatric patients 3 months to 17 years of age.

The clinical development program for ertapenem in pediatric patients consisted of the following studies:

Pharmacokinetic Studies

1. Protocol 028: An Open, Intravenous Study to Evaluate the Plasma Concentration Profiles of MK-0826 in Patients Aged 3 Months Through 17 Years.

   This was an open-label, single intravenous (IV) dose, multicenter, parallel group study in pediatric patients 3 months to 17 years. This study enrolled 84 patients who had with infections requiring antibiotic therapy and hospitalization. Single IV doses of 15, 20 and 40 mg/kg were infused over 30 minutes.

2. Protocol 031/32: An Open, Intravenous Study to Evaluate the Cerebrospinal Fluid Concentration Profiles in Patients 3 Months to 17 Years of Bacterial Meningitis.

   This was an open-label, multicenter, single IV dose study of 15 or 20 mg/kg of ertapenem to evaluate the cerebrospinal fluid concentration profile in pediatric patients 3 months to 17 years of age with bacterial meningitis. There were 13 patients entered into this study.

Safety/Efficacy Studies

3. Protocol 036: A Prospective, Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Local Tolerability, and Clinical Outcome of Ertapenem Sodium (MK-0826) Versus Ceftriaxone Sodium in Pediatric Patients With Complicated Urinary Tract Infection, Skin and Soft Tissue Infection, or Community-Acquired Pneumonia.

   This was a double-blind, randomized, multicenter, comparative study of ertapenem versus ceftriaxone in pediatric patients with complicated urinary tract infection, skin and soft tissue infection, or community-acquired pneumonia. There were 404 patients randomized into this study.

4. 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.

   This was an open-label, multicenter, randomized (3:1 ratio), prospective, comparative study to evaluate safety and tolerability and to assess the efficacy of ertapenem versus ticarcillin/clavulanate in pediatric patients with

complicated intra-abdominal infections and acute pelvic infections. There were 112 patients randomized into this study.

1.3.2 Efficacy

In this pediatric development program, the primary objective was to evaluate the plasma pharmacokinetics and to assess the overall safety and tolerability of ertapenem in indications previously shown to be effectively treated in adults. Pediatric efficacy can be demonstrated by results from the comparator-controlled pediatric studies, supported additionally by data from adequate, well-controlled clinical trials in adults which were the basis of the original approval. The indications studied for ertapenem in children had previously been studied in adequate, well-controlled clinical trials in adults and ertapenem was shown to be generally safe, well-tolerated and efficacious. Therefore, pediatric efficacy in each of these indications was not considered the primary objective for these studies.

For study 036, in the evaluable per protocol (EPP) population, clinical response rates in patients with SSSI were 95.5% (64/67) for ertapenem and 100.0% for ceftriaxone (26/26). In patients with CAP, clinical response rates were 96.1% (74/77) for ertapenem and 96.4% (27/28) for ceftriaxone. In patients with UTI, microbiologic response rates were 87.0% (40/46) for ertapenem and 90.0% (18/20) for ceftriaxone.

For study 038, in the EPP population, clinical response rates in patients with IAI were 83.7% (36/43) for ertapenem and 63.6% (7/11) for ticarcillin/clavulanate. In patients with API, clinical response rates were 100.0% (23/23) for ertapenem and 100.0% (4/4) for ticarcillin/clavulanate.

Overall, the combined (Protocol 036 and Protocol 038) clinical response rate in the EPP analysis for the ertapenem treatment group was 92.7% and 93.5% for the comparators combined. Overall, the combined (Protocol 036 and Protocol 038) microbiologic response rate for the EPP population in the ertapenem treatment group was 88.9% and 89.8% in the comparator groups combined.

The ertapenem response rates in pediatric patients were comparable to the rates observed in clinical studies in adults.

1.3.3 Safety

The primary objective of the pediatric program was to characterize the overall safety and tolerability of ertapenem in pediatric patients treated for infectious disease indications previously studied and currently licensed in adults.

A total of 480 patients ages 3 months to 17 years were treated with ertapenem: 96 patients in the pharmacokinetic studies and 384 patients in the clinical studies. In the clinical studies, the mean duration for patients receiving ertapenem was 4.9 days with a range of 1 to 36 days. Approximately 70% of the patients treated with ertapenem were

switched (as allowed per protocol) from parenteral to an appropriate oral follow-up antimicrobial agent which they received for a mean duration of 8.3 days.

There were a total of 508 patients enrolled in the clinical safety/efficacy trials, 384 in the ertapenem group, 100 in the ceftriaxone group and 24 patients in the ticarcillin/clavulanate group. Safety was assessed by the investigator throughout the study and up to the 14-day posttreatment follow-up visit.

The most common drug-related clinical adverse events are diarrhea, vomiting, infusion-site erythema and infusion-site pain. The most common drug-related laboratory adverse experiences are increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST) and decreased neutrophil count.

The safety profile observed in children is similar to that observed in adults. The specific clinical adverse experiences reported most frequently in the ertapenem group during study therapy and 14-day follow-up were diarrhea (11.7%), vomiting (10.2%), infusion-site pain (7%), pyrexia (4.9%), abdominal pain (4.7%), diaper dermatitis (4.7%), headache (4.4%), and cough (4.4%). Similar frequencies were also reported in the ceftriaxone and ticarcillin/clavulanate groups. In the ertapenem group, diarrhea (6.5%), vomiting (2.1%), infusion-site erythema (2.6%) and infusion-site pain (5.5%) were the most common drug-related adverse events reported.

The serious adverse events and discontinuations due to adverse events were generally comparable between ertapenem and the comparators in these studies, ceftriaxone and ticarcillin/clavulanate.

1.3.4 Dosing Regimen and Administration

The appropriate dosing regimen of ertapenem is 15 mg/kg BID for pediatric patients 3 months to 12 years of age and 1 g once daily for patients 13 to 17 years of age.

Cerebrospinal fluid level concentrations were not adequate to cover all relevant pathogens and pursue bacterial meningitis as an indication. This information is to be included in the label.

1.3.5 Drug-Drug Interactions

No new information regarding drug-drug interactions was identified.

1.3.6 Special Populations

This submission was a response to a Pediatric Written Request.

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/s/

Janice Soreth

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