



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-N-0918]

Pediatric Studies of Meropenem Conducted in Accordance With the Public Health Service Act;
Availability of Summary Report and Requested Labeling Changes

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a summary report of the pediatric studies of meropenem conducted in accordance with the Public Health Service Act (the PHS Act) and is making available requested labeling changes for meropenem. The Agency is making this information available consistent with the PHS Act.

FOR FURTHER INFORMATION CONTACT: Lori Gorski, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 6415, Silver Spring, MD 20993-0002, 301-796-2200, FAX: 301-796-9855, email:

lori.gorski@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Meropenem Summary Review

In the Federal Register of August 13, 2003 (68 FR 48402), meropenem was identified as a drug that needed further study in pediatrics. The approved labeling lacked adequate

information on dosing, pharmacokinetic, tolerability, and safety data in newborns and young infants with complicated intra-abdominal infections.

A written request for pediatric studies of meropenem was issued on September 10, 2004, to AstraZeneca Pharmaceuticals, the holder of the new drug application (NDA) for meropenem. FDA did not receive a response to the written request. Accordingly, the National Institutes of Health (NIH) issued a request for proposals to conduct the pediatric studies described in the written request on August 15, 2005, and awarded funds to Duke University and Stanford University on September 28, 2007, to complete the studies described in the written request.

On completion of the studies, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) submitted a final clinical study report for meropenem to FDA for review under investigational new drug application (IND) 101043: (NICHD-2005-18) "A Multiple Dose PK Study of Meropenem In Young Infants (less than 91 days of age) With Suspected or Complicated Intra-abdominal Infections."

In the Federal Register of February 27, 2012 (77 FR 11556), FDA announced the opening on February 17, 2012, of docket FDA-2011-N-0918 for submission of data from pediatric studies of meropenem. The data submitted to the docket by NIH were submitted in accordance with section 409I of the PHS Act (42 U.S.C. 284m) and were the same data submitted to IND 101043, with the exception that personal privacy information had been redacted from the data submitted to the docket.

The meropenem docket remained opened for public comment from February 27, 2012, until March 28, 2012. There were no comments submitted to the docket during that time.

The key findings of this final clinical study report are:

The submitted study was an open-label, non-comparative, multicenter, prospective, multiple pharmacokinetic (PK) and safety study in infants less than 91 days of age. The study enrolled 200 infants with a median postnatal age of 21 days (range 1 to 92 days) and a median gestation age (GA) of 27.8 weeks (range 22.5 to 40 weeks). Infants with complicated intra-abdominal infections who were receiving meropenem based on local standard of care were eligible for enrollment. Complicated intra-abdominal infections were defined per the protocol as physical, radiologic, or bacteriologic findings of complicated intra-abdominal infection to include peritonitis, necrotizing enterocolitis (NEC) grade II or higher by Bell's criteria, Hirschsprung's disease with perforation, spontaneous perforation, meconium ileus with perforation, bowel obstruction with perforation, as evidenced by free peritoneal air on abdominal radiograph, intestinal pneumatosis, or portal venous gas on abdominal radiographic examination, or possible NEC.

The study was not statistically powered to establish efficacy because the Division of Anti-Infective Products agreed that extrapolation of efficacy to pediatric populations from adult populations was acceptable. However, clinical efficacy endpoints were also evaluated. The efficacy assessment included a comparison of the clinical status at study baseline and at day 28 or after a minimum of 7 days of treatment, using a combination of an assessment using the Score for Neonatal Acute Physiology II tool and other protocol specified outcome criteria. The clinical endpoint was defined as the patient being alive, with negative bacterial cultures from a sterile body fluid, and a presumptive clinical cure. Clinical failure was defined as death, change in antibiotic therapy while on study drug, or lack of presumptive clinical cure. The addition of treatment directed against Gram-positive pathogens from a non-abdominal source was not considered to represent treatment failure. Using these criteria, 195/200 patients or 97.5 percent

were considered to have achieved the clinical endpoint. Of the 195 patients included in the efficacy population, 192 (98.5 percent) were evaluated for efficacy. The overall efficacy success rate for the study was 84.4 percent (95 percent confidence interval, 78.5 to 89.2 percent).

Analysis of safety was a primary objective of the study. The following assessments were included in the study: Monitoring for adverse events, serious adverse events, and death; documentation of seizures; acute abdominal complications; development of resistant bacterial infection or candidiasis; treatment failure; physical examination; clinical laboratory values; cultures from sterile sites, and concomitant medications. There were 11 deaths in the study; all occurred in patients less than 32 weeks GA. The most common cause of death was multi-organ failure. None of the deaths were related to meropenem administration. The following adverse events occurred with a frequency in the study that differed from that seen in previous pediatric and adult studies: Convulsion (seizures), 5 percent, hyperbilirubinemia, 4.5 percent and vomiting, 2.5 percent. Study oversight included a safety committee and an independent data safety monitoring board.

The Division of Anti-Infective Products agreed that meropenem was well-tolerated in the pediatric population enrolled in the study. Of the 10 patients with seizures, 8 patients were adjudicated to have developed seizures possibly due to the study medication. Because cerebrospinal fluid was only evaluated in a limited number of patients with seizures, it is not possible to determine if the seizure threshold may have changed due to possible underlying meningitis and the administration of meropenem.

II. Recommendation

This study supports the use of meropenem in neonates and infants less than 91 days of age for complicated intra-abdominal infections. However, infants with complicated intra-

abdominal infections are anticipated to have different physiological characteristics than patients with meningitis that may impact the PK of meropenem; as such, it may not be appropriate to apply the PK findings from this population to a patient population with meningitis. The Division recommended that the evaluation of meropenem in infants less than 91 days of age be limited to the treatment of complicated intra-abdominal infections at this time.

FDA's requested labeling changes, including dosing recommendations for the use of meropenem in neonates and infants less than 91 days of age for complicated intra-abdominal infections, are available on the FDA Web site at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm379088.htm> and in the docket (Ref. 1).

Dated: May 21, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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