Merrem® IV (meropenem for Injection) NDA 50706

FDA REQUESTED LABELING CHANGES AS PER THE AGENCY REVIEW

Strikeout items have been removed, underline items have been added.

1 INDICATIONS AND USAGE

For information regarding use in pediatric patients see *Indications and Usage* (1.1), (1.2) or (1.3); *Dosage and Administration* (2.3), ~~and~~ *Adverse Reactions* (6.1), and *Clinical Pharmacology* (12.3*)*.

1.1 Intra-abdominal Infections (Adult and Pediatric Patients ~~≥ 3 month of age~~ 3 months of age and older only)

MERREM I.V. is indicated as a single agent therapy for the treatment of complicated skin and skin structure infections due to *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus pyogenes, Streptococcus agalactiae,* viridans group streptococci, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Bacteroides fragilis,* and *Peptostreptococcus* species.

1.2 Intra-abdominal Infections (Adult and Pediatric Patients ~~≥ 3 month of age~~)

MERREM I.V. is indicated as a single agent therapy for the treatment of complicated appendicitis and peritonitis caused by viridans group streptococci, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides fragilis, B. thetaiotaomicron,* and *Peptostreptococcus* species.

1.3 Bacterial Meningitis (Pediatric Patients ~~≥ 3 month of age~~ 3 months of age and older only)

MERREM I.V. is indicated as a single agent therapy for the treatment of bacterial meningitis caused by *Streptococcus pneumoniae‡, Haemophilus influenzae,* and *Neisseria meningitidis.*

‡ The efficacy of meropenem as monotherapy in the treatment of meningitis caused by penicillin nonsusceptible isolates of *Streptococcus pneumoniae* has not been established.

MERREM I.V. has been found to be effective in eliminating concurrent bacteremia in association with bacterial meningitis.

2 DOSAGE AND ADMINISTRATION

2.3 Use in Pediatric Patients ~~(≥ 3 month only)~~

Pediatric Patients 3 Months of Age and Older

For pediatric patients 3 months of age and older, the MERREM I.V. dose is 10 mg/kg, 20 mg/kg or 40 mg/kg every 8 hours (maximum dose is 2 grams every 8 hours), depending on the type of infection (complicated skin and skin structure, intra-abdominal or meningitis). (See dosing table below.) Pediatric patients weighing over 50 kg should be administered MERREM I.V. at a dose of 500 mg every 8 hours for complicated skin and skin structure infections, 1 gram every 8 hours for intra-abdominal infections and 2 grams every 8 hours for meningitis. MERREM I.V. should be given as intravenous infusion over

approximately 15 minutes to 30 minutes or as an intravenous bolus injection (5 mL to 20 mL) over approximately 3 minutes-5 minutes.

There is limited safety data available to support the administration of a 40 mg/kg (up to a maximum of 2 grams) bolus dose.

Recommended MERREM I.V. Dosage Schedule for Pediatric Patients 3 Months of Age and Older with Normal Renal Function			
Type of Infection	Dose (mg/kg)	Up to a Maximum Dose	Dosing Interval
Complicated skin and skin structure	10	500 mg	Every 8 hours
Intra-abdominal	20	1 gram	Every 8 hours
Meningitis	40	2 grams	Every 8 hours

There is no experience in pediatric patients with renal impairment. When treating complicated skin and skin structure infections caused by *P. aeruginosa*, a dose of 20 mg/kg (or 1 gram for pediatric patients weighing over 50 kg) every 8 hours is recommended.

Pediatric Patients Less Than 3 Months of Age

For pediatric patients (with normal renal function) less than 3 months of age, with intra-abdominal infections, the MERREM I.V. dose is based on gestational age (GA) and postnatal age (PNA). (See dosing table below). MERREM I.V. should be given as intravenous infusion over 30 minutes.

Recommended MERREM I.V. Dosage Schedule for Pediatric Patients Less than 3 Months of Age with Complicated Intra-Abdominal Infections and Normal Renal Function		
Age Group	**Dose (mg/kg)**	**Dose Interval**
Infants less than 32 weeks GA and PNA less than 2 weeks	20	Every 12 hours
Infants less than 32 weeks GA and PNA 2 weeks and older	20	Every 8 hours
Infants 32 weeks and older GA and PNA less than 2 weeks	20	Every 8 hours
Infants 32 weeks and older GA and PNA 2 weeks and older	30	Every 8 hours

There is no experience in pediatric patients with renal impairment

6.1 Adverse Reactions from Clinical Trials

Pediatric Patients:

Clinical Adverse Reactions
MERREM I.V. was studied in 515 pediatric patients (3 months to less than 13 years of age) with serious bacterial infections (excluding meningitis, see next section) at dosages of 10 mg/kg to 20 mg/kg every 8 hours. The types of clinical adverse events seen in these patients are similar to the adults, with the most common adverse events reported as possibly, probably, or definitely related to MERREM I.V. and their rates of occurrence as follows:

Diarrhea	3.5%
Rash	1.6%
Nausea and Vomiting	0.8%

MERREM I.V. was studied in 321 pediatric patients (3 months to less than 17 years of age) with meningitis at a dosage of 40 mg/kg every 8 hours. The types of clinical adverse events seen in these patients are similar to the adults, with the most common adverse events reported as possibly, probably, or definitely related to MERREM I.V. and their rates of occurrence as follows:

Diarrhea	4.7%
Rash (mostly diaper area moniliasis)	3.1%
Oral Moniliasis	1.0%
Glossitis	1.0%

MERREM I.V. was studied in 200 neonates and infants less than 3 months of age. The study was open-label, uncontrolled, 98% of the infants received concomitant medications, and the majority of adverse reactions were reported in neonates less than 32 weeks gestational age and critically ill at baseline, making it difficult to assess the relationship of the adverse reactions to MERREM I.V.
The clinical adverse reactions seen in these patients that were reported (regardless of investigator assessment of causality) and their rates of occurrence are as follows:

Convulsion	5.0%
Hyperbilirubinemia (conjugated)	4.5%
Vomiting	2.5%

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

~~The safety and effectiveness of MERREM I.V. have been established for pediatric patients ≥ 3 months of age. Use of MERREM I.V. in pediatric patients with bacterial meningitis is supported by evidence from adequate and well-controlled studies in the pediatric population. Use of MERREM I.V. in pediatric patients with intra-abdominal infections is supported by evidence from adequate and well-controlled studies with adults with additional data from pediatric pharmacokinetics studies and controlled clinical trials in pediatric patients. Use of MERREM I.V. in pediatric patients with complicated skin and skin structure infections is supported by evidence from an adequate and well-controlled study with adults and additional data from pediatric pharmacokinetics studies [*see Indications and Usage* (1.3), *Dosage and Administration* (2.3), *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3) and *Clinical Studies* (14.3)].~~

The safety and effectiveness of MERREM I.V. have been established for pediatric patients 3 months of age and older with complicated skin and skin structure infections and bacterial meningitis, and for pediatric patients of all ages with complicated intra-abdominal infections.

Skin and Skin Structure Infections
Use of MERREM I.V. in pediatric patients 3 months of age and older with complicated skin and skin structure infections is supported by evidence from an adequate and well-controlled study in adults and additional data from pediatric pharmacokinetics studies [*see Indications and Usage (1.3)*, *Dosage and Administration (2.3)*, *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)* and *Clinical Studies (14.1)*].

Intra-abdominal Infections

Use of MERREM I.V. in pediatric patients 3 months of age and older with intra-abdominal infections is supported by evidence from adequate and well-controlled studies in adults with additional data from pediatric pharmacokinetics studies and controlled clinical trials in pediatric patients. Use of MERREM I.V. in pediatric patients less than 3 months of age with intra-abdominal infections is supported by evidence from adequate and well-controlled studies in adults with additional data from a pediatric pharmacokinetic and safety study *[see Indications and Usage (1.2), Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

Bacterial Meningitis
Use of MERREM I.V. in pediatric patients 3 months of age and older with bacterial meningitis is supported by evidence from adequate and well-controlled studies in the pediatric population *[see Indications and Usage (1.3), Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.3)]*.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics
Pediatric Patients

The pharmacokinetics of meropenem for injection I.V., in pediatric patients 2 years of age or older, are similar to those in adults. The elimination half-life for meropenem was approximately 1.5 hours in pediatric patients of age 3 months to 2 years. ~~The pharmacokinetics are linear over the dose range from 10 to 40 mg/kg.~~

The pharmacokinetics of meropenem in patients less than 3 months of age receiving combination antibacterial drug therapy are given below.

Table 2 Meropenem Pharmacokinetic Parameters in Patients Less Than 3 Months of Age*

	GA less than 32 weeks PNA less than 2 weeks (20mg/kg every 12 hours)	GA less than 32 weeks PNA 2 weeks or older (20mg/kg every 8 hours)	GA 32 weeks or older PNA less than 2 weeks (20mg/kg every 8 hours)	GA 32 weeks or older PNA 2 weeks or older (30mg/kg every 8 hours)	Overall
CL (L/h/kg)	0.089	0.122	0.135	0.202	0.119
V (L/kg)	0.489	0.467	0.463	0.451	0.468
AUC0-24 (mcg-h/mL)	448	491	445	444	467
Cmax (mcg/mL)	44.3	46.5	44.9	61	46.9
Cmin (mcg/mL)	5.36	6.65	4.84	2.1	5.65
T1/2 (h)	3.82	2.68	2.33	1.58	2.68
*Values are derived from a population pharmacokinetic analysis of sparse data					