

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 50-706/S-034

Trade Name: MERREM I.V.

Generic Name: meropenem for injection

Sponsor: AstraZeneca Pharmaceuticals, LP

Approval Date: December 16, 2013

Indication: single agent therapy for the treatment of:
Complicated skin and skin structure infections,
complicated intra-abdominal, and bacterial meningitis.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 50-706/S-034

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-706/S-034

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 050706/S-032
NDA 050706/S-034

SUPPLEMENT APPROVAL

AstraZeneca Pharmaceuticals LP
Attention: Cynthia S. Dommissie, Pharm.D.
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Dommissie:

Please refer to your Supplemental New Drug Applications (sNDA), S-032 dated and received February 28, 2013, and S-034, dated and received July 18, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for MERREM I.V. (meropenem for injection)

We acknowledge receipt of your amendments dated April 10 and November 14, 2013 for S-032, and December 3, 2013 for S-034.

S-032: This "Prior Approval" labeling supplement provides for revisions to Section 2, **DOSAGE AND ADMINISTRATION**, regarding adult and pediatric dosing information for the treatment of complicated skin and skin structure infections due to *Pseudomonas aeruginosa*, and Section 12, **CLINICAL PHARMACOLOGY**, Subsection 12.4, **Microbiology**, regarding susceptibility interpretive criteria for *P. aeruginosa*.

S-034: This "Changes Being Effected" labeling supplement updates Section 2, **DOSAGE AND ADMINISTRATION**, Subsection 2.6, **Stability and Storage**, and Section 8, **USE IN SPECIFIC POPULATIONS**, Subsection 8.3, **Nursing Mothers**.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susmita Samanta, Safety Regulatory Project Manager, at (301) 796-0803.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:

Content of Labeling

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

/s/

SUMATHI NAMBIAR
12/16/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-706/S-034

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MERREM I.V. safely and effectively. See full prescribing information for MERREM I.V.

MERREM® I.V. (meropenem for Injection)
Initial U.S. Approval: 1996

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MERREM I.V. and other antibacterial drugs, MERREM I.V. should only be used to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

RECENT MAJOR CHANGES

Dosage and Administration, Adult Patients (2.1)
Dosage and Administration, Use in Pediatric Patients (≥ 3 Months only) (2.3)
Stability and storage (2.6)

INDICATIONS AND USAGE

MERREM I.V. is a penem antibacterial indicated as single agent therapy for the treatment of:

- Complicated skin and skin structure infections (adult patients and pediatric patients ≥ 3 months only). (1.1)
- Complicated intra-abdominal infections (adult patients and pediatric patients ≥ 3 months only). (1.2)
- Bacterial meningitis (pediatric patients ≥ 3 months only). (1.3)

DOSAGE AND ADMINISTRATION

- 500 mg every 8 hours by intravenous infusion over 15 to 30 minutes for skin and skin structure infections for adult patients. When treating infections caused by *Pseudomonas aeruginosa*, a dose of 1g every 8 hours is recommended (2.1).
- 1 g every 8 hours by intravenous infusion over 15 to 30 minutes for intra-abdominal infections for adult patients. (2.1)
- 1 g every 8 hours by intravenous bolus injection (5 to 20 mL) over 3 to 5 minutes for adult patients. (2.1)
- Dosage should be reduced in adult patients with renal impairment. (2.2)

| Recommended MERREM I.V. Dosage Schedule for Adult Patients with Renal Impairment | | |
|--|--|-----------------|
| Creatinine Clearance (mL/min) | Dose (dependent on type of infection) | Dosing Interval |
| > 50 | Recommended dose (500 mg cSSI and 1 g Intra-abdominal) | Every 8 hours |
| 26-50 | Recommended dose | Every 12 hours |
| 10-25 | One-half recommended dose | Every 12 hours |
| <10 | One-half recommended dose | Every 24 hours |

- Pediatric patients ≥ 3 months of age. (2.3)

| Recommended MERREM I.V. Dosage Schedule for Pediatric Patients 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 g | Every 8 hours |
| Meningitis | 40 | 2 g | Every 8 hours |
| - Intravenous infusion is to be given over approximately 15 to 30 minutes. - Intravenous bolus injection (5 to 20 mL) is to be given over approximately 3-5 minutes. - There is no experience in pediatric patients with renal impairment. | | | |

*20 mg/kg (or 1 g for pediatric patients weighing over 50 kg) every 8 hours is recommended when treating complicated skin and skin structure infections caused by *P. aeruginosa* (2.3).

DOSAGE FORMS AND STRENGTHS

500 mg Injection Vial (3)

1 g Injection Vial (3)

CONTRAINDICATIONS

- Known hypersensitivity to product components or anaphylactic reactions to β-lactams. (4)

WARNINGS AND PRECAUTIONS

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving β-lactams. (5.1)
- Seizures and other adverse CNS experiences have been reported during treatment. (5.2)
- Co-administration of MERREM I.V. with valproic acid or divalproex sodium reduces the serum concentration of valproic acid potentially increasing the risk of breakthrough seizures. (5.3, 7.2)
- *Clostridium difficile*-associated diarrhea (ranging from mild diarrhea to fatal colitis) has been reported. Evaluate if diarrhea occurs. (5.4)
- In patients with renal dysfunction, thrombocytopenia has been observed. (5.8)

ADVERSE REACTIONS

Most common adverse reactions (≥ 2%) are: headache, nausea, constipation, diarrhea, anemia, vomiting, and rash (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch for voluntary reporting of adverse reactions.

DRUG INTERACTIONS

- Co-administration of MERREM I.V. with probenecid inhibits renal excretion of meropenem (7.1)
- Co-administration of MERREM I.V. with valproic acid or divalproex sodium reduces the serum concentration of valproic acid potentially increasing the risk of breakthrough seizures. (5.3, 7.2)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: Dose adjustment is necessary, if creatinine clearance is 50 mL/min or less. (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2013

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- 1.1 Skin and Skin Structure Infections (Adult Patients and Pediatric Patients ≥ 3 Months only)
- 1.2 Intra-abdominal Infections (Adult Patients and Pediatric Patients ≥ 3 Months only)
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MERREM I.V. and other antibacterial drugs, MERREM I.V. should only be used to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

MERREM I.V. is useful as presumptive therapy in the indicated condition (e.g. intra-abdominal infections) prior to the identification of the causative organisms because of its broad spectrum of bactericidal activity.

1.1 Skin and Skin Structure Infections (Adult Patients and Pediatric Patients \geq 3 Months 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 Patients and Pediatric Patients \geq 3 Months only)

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 \geq 3 Months 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.

For information regarding use in pediatric patients (3 months of age and older) [see *Indications and Usage* (1.1), (1.2) or (1.3); *Dosage and Administration* (2.3), and *Adverse Reactions* (6.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Adult Patients

The recommended dose of MERREM I.V. is 500 mg given every 8 hours for skin and skin structure infections and 1 g given every 8 hours for intra-abdominal infections. When treating complicated skin and skin structure infections caused by *P.aeruginosa*, a dose of 1g every 8 hours is recommended.

MERREM I.V. should be administered by intravenous infusion over approximately 15 to 30 minutes. Doses of 1 g may also be administered as an intravenous bolus injection (5 to 20 mL) over approximately 3-5 minutes.

2.2 Use in Adult Patients with Renal Impairment

Dosage should be reduced in patients with creatinine clearance of 50 mL/min or less. (See dosing table below.)

When only serum creatinine is available, the following formula (Cockcroft and Gault equation)⁵ may be used to estimate creatinine clearance.

Males: Creatinine Clearance (mL/min) =

$$\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.85 x above value

Recommended MERREM I.V. Dosage Schedule for Adult Patients With Renal Impairment

| Creatinine Clearance (mL/min) | Dose (dependent on type of infection) | Dosing Interval |
|-------------------------------|--|-----------------|
| > 50 | Recommended dose (500 mg cSSSI and 1g Intra-abdominal) | Every 8 hours |
| >25-50 | Recommended dose | Every 12 hours |
| 10-25 | One-half recommended dose | Every 12 hours |
| <10 | One-half recommended dose | Every 24 hours |

There is inadequate information regarding the use of MERREM I.V. in patients on hemodialysis or peritoneal dialysis.

2.3 Use in Pediatric Patients (≥ 3 Months only)

For pediatric patients from 3 months of age and older, the MERREM I.V. dose is 10, 20 or 40 mg/kg every 8 hours (maximum dose is 2 g 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 g every 8 hours for intra-abdominal infections and 2 g every 8 hours for meningitis. MERREM I.V. should be given as intravenous infusion over approximately 15 to 30 minutes or as an intravenous bolus injection (5 to 20 mL) over approximately 3-5 minutes.

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

Recommended MERREM I.V. Dosage Schedule for Pediatric Patients 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 g | Every 8 hours |
| Meningitis | 40 | 2 g | Every 8 hours |

When treating complicated skin and skin structure infections caused by *P. aeruginosa*, a dose of 20 mg/kg (or 1 g for pediatric patients weighing over 50 kg) every 8 hours is recommended.

There is no experience in pediatric patients with renal impairment.

2.4 Preparation of Solution

For Intravenous Bolus Administration

Constitute injection vials (500 mg and 1 g) with sterile Water for Injection (see table below). Shake to dissolve and let stand until clear.

| Vial Size | Amount of Diluent Added (mL) | Approximate Withdrawable Volume (mL) | Approximate Average Concentration (mg/mL) |
|-----------|------------------------------|--------------------------------------|---|
| 500 mg | 10 | 10 | 50 |
| 1 g | 20 | 20 | 50 |

For Infusion

Infusion vials (500 mg and 1 g) may be directly constituted with a compatible infusion fluid. Alternatively, an injection vial may be constituted, then the resulting solution added to an I.V. container and further diluted with an appropriate infusion fluid [see *Dosage and Administration* (2.5) and (2.6)].

WARNING: Do not use flexible container in series connections.

2.5 Compatibility

Compatibility of MERREM I.V. with other drugs has not been established. MERREM I.V. should not be mixed with or physically added to solutions containing other drugs.

2.6 Stability and Storage

Freshly prepared solutions of MERREM I.V. should be used. However, constituted solutions of MERREM I.V. maintain satisfactory potency under the conditions described below. Solutions of intravenous MERREM I.V. should not be frozen.

Intravenous Bolus Administration

MERREM I.V. injection vials constituted with sterile Water for Injection for bolus administration (up to 50 mg/mL of MERREM I.V.) may be stored for up to 3 hours at up to 25°C (77°F) or for 13 hours at up to 5°C (41°F).

Solutions prepared for infusion (MERREM I.V. concentrations ranging from 1 to 20 mg/mL) constituted with Sodium Chloride Injection 0.9% may be stored for 1 hour at up to 25°C (77°F) or 15 hours at up to 5°C (41°F).

Solutions prepared for infusion (MERREM I.V. concentrations ranging from 1 to 20 mg/mL) constituted with Dextrose Injection 5% should be used immediately.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

3 DOSAGE FORMS AND STRENGTHS

Single use clear glass vials containing 500 mg or 1 g (as the trihydrate blend with anhydrous sodium carbonate for constitution) of sterile meropenem powder.

4 CONTRAINDICATIONS

MERREM I.V. is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to β -lactams.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with β -lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens.

There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with another β -lactam. Before initiating therapy with MERREM I.V., careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other β -lactams, and other allergens. If an allergic reaction to MERREM I.V. occurs, discontinue the drug immediately. Serious anaphylactic reactions require immediate emergency treatment with epinephrine, oxygen, intravenous steroids, and airway management, including intubation. Other therapy may also be administered as indicated.

5.2 Seizure Potential

Seizures and other adverse CNS experiences have been reported during treatment with MERREM I.V. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) or with bacterial meningitis and/or compromised renal function [*see Adverse Reactions (6.1) and Drug Interactions (7.2)*].

During clinical investigations, 2904 immunocompetent adult patients were treated for non-CNS infections with the overall seizure rate being 0.7% (based on 20 patients with this adverse event). All meropenem-treated patients with seizures had pre-existing contributing factors. Among these are included prior history of seizures or CNS abnormality and concomitant medications with seizure potential. Dosage adjustment is recommended in patients with advanced age and/or reduced renal function [*see Dosage and Administration (2.2)*].

Close adherence to the recommended dosage regimens is urged, especially in patients with known factors that predispose to convulsive activity. Anti-convulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anti-convulsant therapy if not already instituted, and the dosage of MERREM I.V. re-examined to determine whether it should be decreased or the antibiotic discontinued.

5.3 Interaction with Valproic Acid

Case reports in the literature have shown that co-administration of carbapenems, including meropenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. Increasing the dose of valproic acid or divalproex sodium may not be sufficient to overcome this interaction. The concomitant use of meropenem and valproic acid or divalproex sodium is generally not recommended. Antibacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of MERREM I.V. is necessary, supplemental anti-convulsant therapy should be considered [*see Drug Interactions (7.2)*].

5.4 *Clostridium difficile*–Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including MERREM I.V., and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.5 Development of Drug-Resistant Bacteria

Prescribing MERREM I.V. in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.6 Overgrowth of Nonsusceptible Organisms

As with other broad-spectrum antibiotics, prolonged use of meropenem may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

5.7 Laboratory Tests

While MERREM I.V. possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

5.8 Patients with Renal Impairment

In patients with renal impairment, thrombocytopenia has been observed but no clinical bleeding reported [*see Dosage and Administration* (2.2), *Adverse Reactions* (6.1), *Use In Specific Populations* (8.5) and (8.6), and *Clinical Pharmacology* (12.3)].

5.9 Dialysis

There is inadequate information regarding the use of MERREM I.V. in patients on hemodialysis or peritoneal dialysis.

5.10 Potential for Neuromotor Impairment

Patients receiving MERREM I.V. on an outpatient basis may develop adverse events such as seizures, headaches and/or paresthesias that could interfere with mental alertness and/or cause motor impairment. Until it is reasonably well established that MERREM I.V. is well tolerated, patients should not operate machinery or motorized vehicles [*see Adverse Reactions* (6.1)].

6 ADVERSE REACTIONS

The following are discussed in greater detail in other sections of labeling:

- Hypersensitivity Reactions [*see Warnings and Precautions* (5.1)]
- Seizure Potential [*see Warnings and Precautions* (5.2)]
- Interaction with Valproic Acid [*see Warnings and Precautions* (5.3)]

- *Clostridium difficile* – Associated Diarrhea [see Warnings and Precautions (5.4)]
- Development of Drug-Resistant Bacteria [see Warnings and Precautions (5.5)]
- Overgrowth of Nonsusceptible Organisms [see Warnings and Precautions (5.6)]
- Laboratory Tests [see Warnings and Precautions (5.7)]
- Patients with Renal Impairment [see Warnings and Precautions (5.8)]
- Dialysis [see Warnings and Precautions (5.9)]
- Potential for Neuromotor Impairment [see Warnings and Precautions (5.10)]

6.1 Adverse Reactions from Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Patients:

During clinical investigations, 2904 immunocompetent adult patients were treated for non-CNS infections with MERREM I.V. (500 mg or 1000 mg every 8 hours). Deaths in 5 patients were assessed as possibly related to meropenem; 36 (1.2%) patients had meropenem discontinued because of adverse events. Many patients in these trials were severely ill and had multiple background diseases, physiological impairments and were receiving multiple other drug therapies. In the seriously ill patient population, it was not possible to determine the relationship between observed adverse events and therapy with MERREM I.V.

The following adverse reaction frequencies were derived from the clinical trials in the 2904 patients treated with MERREM I.V.

Local Adverse Reactions

Local adverse reactions that were reported irrespective of the relationship to therapy with MERREM I.V. were as follows:

| | |
|------------------------------------|------|
| Inflammation at the injection site | 2.4% |
| Injection site reaction | 0.9% |
| Phlebitis/thrombophlebitis | 0.8% |
| Pain at the injection site | 0.4% |
| Edema at the injection site | 0.2% |

Systemic Adverse Reactions

Systemic adverse reactions that were reported irrespective of the relationship to MERREM I.V. occurring in greater than 1.0% of the patients were diarrhea (4.8%), nausea/vomiting (3.6%), headache (2.3%), rash (1.9%), sepsis (1.6%), constipation (1.4%), apnea (1.3%), shock (1.2%), and pruritus (1.2%).

Additional systemic adverse reactions that were reported irrespective of relationship to therapy with MERREM I.V. and occurring in less than or equal to 1.0% but greater than 0.1% of the patients are listed below within each body system in order of decreasing frequency:

Bleeding events were seen as follows: gastrointestinal hemorrhage (0.5%), melena (0.3%), epistaxis (0.2%), hemoperitoneum (0.2%), summing to 1.2%.

Body as a Whole: pain, abdominal pain, chest pain, fever, back pain, abdominal enlargement, chills, pelvic pain

Cardiovascular: heart failure, heart arrest, tachycardia, hypertension, myocardial infarction, pulmonary embolus, bradycardia, hypotension, syncope

Digestive System: oral moniliasis, anorexia, cholestatic jaundice/jaundice, flatulence, ileus, hepatic failure, dyspepsia, intestinal obstruction

Hemic/Lymphatic: anemia, hypochromic anemia, hypervolemia

Metabolic/Nutritional: peripheral edema, hypoxia

Nervous System: insomnia, agitation/delirium, confusion, dizziness, seizure, nervousness, paresthesia, hallucinations, somnolence, anxiety, depression, asthenia [*see Warnings and Precautions* (5.2) and (5.10)].

Respiratory: respiratory disorder, dyspnea, pleural effusion, asthma, cough increased, lung edema

Skin and Appendages: urticaria, sweating, skin ulcer

Urogenital System: dysuria, kidney failure, vaginal moniliasis, urinary incontinence

Adverse Laboratory Changes

Adverse laboratory changes that were reported irrespective of relationship to MERREM I.V. and occurring in greater than 0.2% of the patients were as follows:

Hepatic: increased SGPT (ALT), SGOT (AST), alkaline phosphatase, LDH, and bilirubin

Hematologic: increased platelets, increased eosinophils, decreased platelets, decreased hemoglobin, decreased hematocrit, decreased WBC, shortened prothrombin time and shortened partial thromboplastin time, leukocytosis, hypokalemia

Renal: increased creatinine and increased BUN

NOTE: For patients with varying degrees of renal impairment, the incidence of heart failure, kidney failure, seizure and shock reported irrespective of relationship to MERREM I.V., increased in patients with moderately severe renal impairment (creatinine clearance >10 to 26 mL/min) [*see Dosage and Administration* (2.2), *Warnings and Precautions* (5.8), *Use in Specific Populations* (8.5) and (8.6) and *Clinical Pharmacology* (12.3)].

Urinalysis: presence of red blood cells

Complicated Skin and Skin Structure Infections

In a study of complicated skin and skin structure infections, the adverse reactions were similar to those listed above. The most common adverse events occurring in >5% of the patients were: headache (7.8%), nausea (7.8%), constipation (7.0%), diarrhea (7.0%), anemia (5.5%), and pain (5.1%). Adverse events with an incidence of >1%, and not listed above, include: pharyngitis, accidental injury, gastrointestinal disorder, hypoglycemia, peripheral vascular disorder, and pneumonia.

Pediatric Patients

Clinical Adverse Reactions

MERREM I.V. was studied in 515 pediatric patients (≥ 3 months to < 13 years of age) with serious bacterial infections (excluding meningitis, see next section) at dosages of 10 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 < 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 | 1.9% |
| Glossitis | 1.0% |

In the meningitis studies, the rates of seizure activity during therapy were comparable between patients with no CNS abnormalities who received meropenem and those who received comparator agents (either cefotaxime or ceftriaxone). In the MERREM I.V. treated group, 12/15 patients with seizures had late onset seizures (defined as occurring on day 3 or later) versus 7/20 in the comparator arm.

Adverse Laboratory Changes

Laboratory changes seen in the pediatric studies, including the meningitis studies, were similar to those reported in the adult studies.

There is no experience in pediatric patients with renal impairment.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of MERREM I.V. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Worldwide post-marketing adverse reactions not otherwise listed in the Adverse Reactions section of this product label and reported as possibly, probably, or definitely drug related are listed within each body system in order of decreasing severity. Hematologic - agranulocytosis, neutropenia, and leukopenia; a positive direct or indirect Coombs test, and hemolytic anemia. Skin-toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, and erythema multiforme.

7 DRUG INTERACTIONS

7.1 Probenecid

Probenecid competes with meropenem for active tubular secretion, resulting in increased plasma concentrations of meropenem. Co-administration of probenecid with meropenem is not recommended.

7.2 Valproic Acid

Case reports in the literature have shown that co-administration of carbapenems, including meropenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. Although the mechanism of this interaction is unknown, data from *in vitro* and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the serum concentrations of valproic acid. If administration of MERREM I.V. is necessary, then supplemental anti-convulsant therapy should be considered [see *Warnings and Precautions* (5.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproductive studies have been performed with meropenem in rats at doses of up to 1000 mg/kg/day, and cynomolgus monkeys at doses of up to 360 mg/kg/day (on the basis of AUC comparisons, approximately 1.8 times and 3.7 times, respectively, to the human exposure at the usual dose of 1 g every 8 hours). These studies revealed no evidence of impaired fertility or harm to the fetus due to meropenem, although there were slight changes in fetal body weight at doses of 250 mg/kg/day (on the basis of AUC comparisons, 0.4 times the human exposure at a dose of 1 g every 8 hours) and above in rats. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Meropenem has been reported to be excreted in human milk. Caution should be exercised when MERREM I.V. is administered to a nursing woman.

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)].

8.5 Geriatric Use

Of the total number of subjects in clinical studies of MERREM I.V., approximately 1100 (30%) were 65 years of age and older, while 400 (11%) were 75 years and older. Additionally, in a study of 511 patients with complicated skin and skin structure infections, 93 (18%) were 65 years of age and older, while 38 (7%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects; spontaneous reports and other reported clinical experience have not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Meropenem is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with renal impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

A pharmacokinetic study with MERREM I.V. in elderly patients has shown a reduction in the plasma clearance of meropenem that correlates with age-associated reduction in creatinine clearance [see *Clinical Pharmacology* (12.3)].

8.6 Patients with Renal Impairment

Dosage adjustment is necessary in patients with creatinine clearance 50 mL/min or less) [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.8), and *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

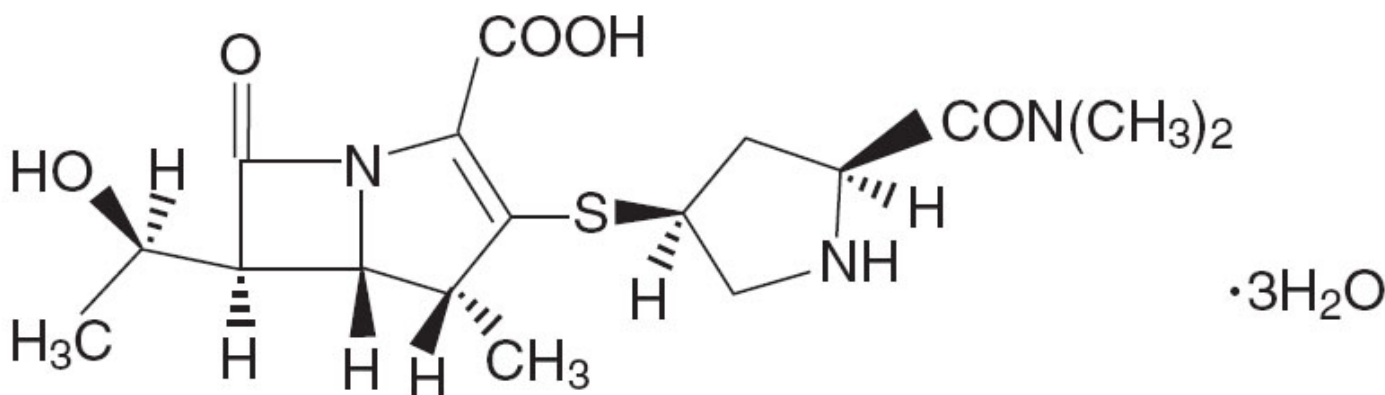
In mice and rats, large intravenous doses of meropenem (2200-4000 mg/kg) have been associated with ataxia, dyspnea, convulsions, and mortalities.

Intentional overdosing of MERREM I.V. is unlikely, although accidental overdosing might occur if large doses are given to patients with reduced renal function. The largest dose of meropenem administered in clinical trials has been 2 g given intravenously every 8 hours. At this dosage, no adverse pharmacological effects or increased safety risks have been observed.

Limited post-marketing experience indicates that if adverse events occur following overdosage, they are consistent with the adverse event profile described in the Adverse Reactions section and are generally mild in severity and resolve on withdrawal or dose reduction. Symptomatic treatments should be considered. In individuals with normal renal function, rapid renal elimination takes place. Meropenem and its metabolite are readily dialyzable and effectively removed by hemodialysis; however, no information is available on the use of hemodialysis to treat overdosage.

11 DESCRIPTION

MERREM® I.V. (meropenem for injection) is a sterile, pyrogen-free, synthetic, broad-spectrum, carbapenem antibiotic for intravenous administration. It is (4R,5S,6S)-3- [[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6- [(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate. Its empirical formula is $C_{17}H_{25}N_3O_5S \cdot 3H_2O$ with a molecular weight of 437.52. Its structural formula is:



MERREM I.V. is a white to pale yellow crystalline powder. The solution varies from colorless to yellow depending on the concentration. The pH of freshly constituted solutions is between 7.3 and 8.3. Meropenem is soluble in 5% monobasic potassium phosphate solution, sparingly soluble in water, very slightly soluble in hydrated ethanol, and practically insoluble in acetone or ether.

When constituted as instructed, each 1 g MERREM I.V. vial will deliver 1 g of meropenem and 90.2 mg of sodium as sodium carbonate (3.92 mEq). Each 500 mg MERREM I.V. vial will deliver 500 mg meropenem and 45.1 mg of sodium as sodium carbonate (1.96 mEq) [see *Dosage and Administration* (2.4)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Meropenem is an antibacterial drug [see *Clinical Pharmacology* (12.4)].

12.3 Pharmacokinetics

Plasma Concentrations

At the end of a 30-minute intravenous infusion of a single dose of MERREM I.V. in healthy volunteers, mean peak plasma concentrations of meropenem are approximately 23 mcg/mL (range 14-26) for the 500 mg dose and 49 mcg/mL (range 39-58) for the 1 g dose. A 5-minute intravenous bolus injection of MERREM I.V. in healthy volunteers results in

mean peak plasma concentrations of approximately 45 mcg/mL (range 18-65) for the 500 mg dose and 112 mcg/mL (range 83-140) for the 1 g dose.

Following intravenous doses of 500 mg, mean plasma concentrations of meropenem usually decline to approximately 1 mcg/mL at 6 hours after administration.

No accumulation of meropenem in plasma was observed with regimens using 500 mg administered every 8 hours or 1 g administered every 6 hours in healthy volunteers with normal renal function.

Distribution

The plasma protein binding of meropenem is approximately 2%.

Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid, achieving concentrations matching or exceeding those required to inhibit most susceptible bacteria. After a single intravenous dose of MERREM I.V., the highest mean concentrations of meropenem were found in tissues and fluids at 1 hour (0.5 to 1.5 hours) after the start of infusion, except where indicated in the tissues and fluids listed in the table below.

Table 1. Meropenem Concentrations in Selected Tissues (Highest Concentrations Reported)

| Tissue | I.V. Dose (g) | Number of Samples | Mean [$\mu\text{g/mL}$ or mcg/(g)] ¹ | Range [$\mu\text{g/mL}$ or mcg/(g)] |
|---------------------------------|-----------------------|-------------------|--|--|
| Endometrium | 0.5 | 7 | 4.2 | 1.7–10.2 |
| Myometrium | 0.5 | 15 | 3.8 | 0.4–8.1 |
| Ovary | 0.5 | 8 | 2.8 | 0.8–4.8 |
| Cervix | 0.5 | 2 | 7.0 | 5.4–8.5 |
| Fallopian tube | 0.5 | 9 | 1.7 | 0.3–3.4 |
| Skin | 0.5 | 22 | 3.3 | 0.5–12.6 |
| Interstitial fluid ² | 0.5 | 9 | 5.5 | 3.2–8.6 |
| Skin | 1.0 | 10 | 5.3 | 1.3–16.7 |
| Interstitial fluid ² | 1.0 | 5 | 26.3 | 20.9–37.4 |
| Colon | 1.0 | 2 | 2.6 | 2.5–2.7 |
| Bile | 1.0 | 7 | 14.6 (3 h) | 4.0–25.7 |
| Gall bladder | 1.0 | 1 | — | 3.9 |
| Peritoneal fluid | 1.0 | 9 | 30.2 | 7.4–54.6 |
| Lung | 1.0 | 2 | 4.8 (2 h) | 1.4–8.2 |
| Bronchial mucosa | 1.0 | 7 | 4.5 | 1.3–11.1 |
| Muscle | 1.0 | 2 | 6.1 (2 h) | 5.3–6.9 |
| Fascia | 1.0 | 9 | 8.8 | 1.5–20 |
| Heart valves | 1.0 | 7 | 9.7 | 6.4–12.1 |
| Myocardium | 1.0 | 10 | 15.5 | 5.2–25.5 |
| CSF (inflamed) | 20 mg/kg ³ | 8 | 1.1 (2 h) | 0.2–2.8 |
| | 40 mg/kg ⁴ | 5 | 3.3 (3 h) | 0.9–6.5 |
| CSF (uninflamed) | 1.0 | 4 | 0.2 (2 h) | 0.1–0.3 |

1. at 1 hour unless otherwise noted
2. obtained from blister fluid
3. in pediatric patients of age 5 months to 8 years
4. in pediatric patients of age 1 month to 15 years

Metabolism

There is one metabolite of meropenem that is microbiologically inactive.

Excretion

In subjects with normal renal function, the elimination half-life of meropenem is approximately 1 hour.

Meropenem is primarily excreted unchanged by the kidneys. Approximately 70% (50 – 75%) of the dose is excreted unchanged within 12 hours. A further 28% is recovered as the microbiologically inactive metabolite. Fecal elimination represents only approximately 2% of the dose. The measured renal clearance and the effect of probenecid show that meropenem undergoes both filtration and tubular secretion.

Urinary concentrations of meropenem in excess of 10 mcg/mL are maintained for up to 5 hours after a 500 mg dose.

Specific Populations

Renal Impairment

Pharmacokinetic studies with MERREM I.V. in patients with renal impairment have shown that the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment (creatinine clearance 50 mL/min or less) [*see Dosage and Administration (2.2) and Use In Specific Populations (8.6)*].

Meropenem I.V. is hemodialyzable. However, there is no information on the usefulness of hemodialysis to treat overdosage [*see Overdosage (10)*].

Hepatic Impairment

A pharmacokinetic study with MERREM I.V. in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem.

Geriatric Patients

A pharmacokinetic study with MERREM I.V. in elderly patients with renal impairment showed a reduction in plasma clearance of meropenem that correlates with age-associated reduction in creatinine clearance.

Pediatric Patients

The pharmacokinetics of meropenem in pediatric patients 2 years of age or older are essentially 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.

Drug Interactions

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem. Following administration of probenecid with meropenem, the mean systemic exposure increased 56% and the mean elimination half-life increased 38%. Co-administration of probenecid with meropenem is not recommended.

12.4 Microbiology

Mechanism of Action

The bactericidal activity of meropenem results from the inhibition of cell wall synthesis. Meropenem readily penetrates the cell wall of most Gram-positive and Gram-negative bacteria to reach penicillin-binding-protein (PBP) targets. Its strongest affinities are toward PBPs 2, 3 and 4 of *Escherichia coli* and *Pseudomonas aeruginosa*; and PBPs 1, 2 and 4 of *Staphylococcus aureus*. Bactericidal concentrations (defined as a 3 log₁₀ reduction in cell counts within 12 to 24 hours) are typically 1-2 times the bacteriostatic concentrations of meropenem, with the exception of *Listeria monocytogenes*, against which lethal activity is not observed.

Meropenem has significant stability to hydrolysis by β -lactamases, both penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria.

Meropenem should not be used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE).

Mechanism of Resistance

There are several mechanisms of resistance to carbapenems: 1) decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) causing reduced bacterial uptake, 2) reduced affinity of the target PBPs, 3) increased expression of efflux pump components, and 4) production of antibiotic-destroying enzymes (carbapenemases, metallo- β -lactamases). Localized clusters of infections due to carbapenem-resistant bacteria have been reported in some regions.

Cross-Resistance

Cross-resistance is sometimes observed with isolates resistant to other carbapenems.

Interactions with Other Antibiotics

In vitro tests show meropenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa*.

Spectrum of Activity

Meropenem has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section (1).

Gram-positive bacteria

Enterococcus faecalis (vancomycin-susceptible isolates only)

Staphylococcus aureus (methicillin-susceptible isolates only)

Streptococcus agalactiae

Streptococcus pneumoniae (penicillin-susceptible isolates only)

Streptococcus pyogenes

Viridans group streptococci

Gram-negative bacteria

Escherichia coli

Haemophilus influenzae

Klebsiella pneumoniae

Neisseria meningitidis

Pseudomonas aeruginosa

Proteus mirabilis

Anaerobic bacteria

Bacteroides fragilis

Bacteroides thetaiotaomicron

Peptostreptococcus species

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following bacteria have exhibited *in vitro* minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoints for meropenem. However, the safety and effectiveness of meropenem in treating clinical infections due to these bacteria have not been established in adequate and well-controlled trials.

Gram-positive bacteria

Staphylococcus epidermidis (methicillin-susceptible isolates only)

Gram-negative bacteria

Aeromonas hydrophila

Campylobacter jejuni
Citrobacter koseri (formerly *diversus*)
Citrobacter freundii
Enterobacter cloacae
Hafnia alvei
Klebsiella oxytoca
Moraxella catarrhalis
Morganella morganii
Pasteurella multocida
Proteus vulgaris
Serratia marcescens

Anaerobic bacteria

Bacteroides distasonis
Bacteroides ovatus
Bacteroides uniformis
Bacteroides ureolyticus
Bacteroides vulgatus
Clostridium difficile
Clostridium perfringens
Eubacterium lentum
Fusobacterium species
Prevotella bivia
Prevotella intermedia
Prevotella melaninogenica
Porphyromonas asaccharolytica
Propionibacterium acnes

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method. Standardized procedures are based on a dilution method¹⁻³ (broth or agar) or equivalent using standardized inoculum concentrations and standardized concentrations of meropenem powder. The MIC values should be interpreted according to the criteria provided in Table 2.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method^{2,3} and requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10-mcg of meropenem to test the susceptibility of microorganisms to meropenem. The disk diffusion interpretive criteria are provided in Table 2.

Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to meropenem as MICs can be determined by a standardized test method^{2,4}. The MIC values obtained should be interpreted according to the criteria provided in Table 2.

Table 2. Susceptibility Interpretive Criteria for Meropenem

| Pathogen | Minimum Inhibitory Concentrations (mcg/mL) | | | Disk Diffusion (zone diameters in mm) | | |
|--|--|-----|-----|---------------------------------------|-------|-----|
| | S | I | R | S | I | R |
| <i>Enterobacteriaceae</i> | ≤1 | 2 | ≥4 | ≥23 | 20-22 | ≤19 |
| <i>Pseudomonas aeruginosa</i> ^a | ≤2 | 4 | ≥8 | ≥19 | 16-18 | ≤15 |
| <i>Haemophilus influenzae</i> ^b | ≤0.5 | — | — | ≥20 | — | — |
| <i>Neisseria meningitidis</i> ^b | ≤0.25 | — | — | ≥30 | — | — |
| <i>Streptococcus pneumoniae</i> ^{c,e} | ≤0.25 | 0.5 | ≥1 | — | — | — |
| <i>Streptococcus agalactiae</i> and <i>Streptococcus pyogenes</i> ^{b,d,e} | ≤0.5 | — | — | — | — | — |
| Anaerobes ^f | ≤4 | 8 | ≥16 | — | — | — |

S = Susceptible, I = Intermediate, R = Resistant

No interpretative criteria have been established for testing enterococci.

Susceptibility of staphylococci to meropenem may be deduced from testing penicillin and either cefoxitin or oxacillin.

^aThe interpretive criteria for *P. aeruginosa* are based upon the dosing of 1g every 8 hours

^bThe current absence of data on resistant isolates precludes defining any category other than “Susceptible”. If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional testing.

^cFor nonmeningitis isolates of *S. pneumoniae* a penicillin MIC of ≤ 0.06 mcg/mL or oxacillin zone ≥ 20 mm can predict susceptibility to meropenem. MIC testing should be performed on isolates that do not test as susceptible by either of these methods, and on all meningitis *S. pneumoniae* isolates.

^dViridans group streptococci should be tested for meropenem susceptibility using an MIC method and results should be reported using the interpretive criteria listed for *S. agalactiae* and *S. pyogenes*.

^eReliable disk diffusion tests for meropenem do not yet exist for testing streptococci

^fMIC values using either Brucella blood or Wilkins Chalgren agar (former reference medium) are considered equivalent, based upon published *in vitro* literature and a multicenter collaborative trial for these antimicrobial agents. Broth microdilution is only recommended for testing the *B. fragilis* group. MIC values for agar or broth microdilution are considered equivalent for that group.

A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of *Intermediate* indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard meropenem powder should provide the following range of values noted in Table 3.

Table 3. Acceptable Quality Control Ranges for Meropenem

| QC Strain | Minimum Inhibitory Concentrations (MICs = mcg/mL) | Disk Diffusion (Zone diameters in mm) |
|--|---|---------------------------------------|
| <i>Staphylococcus aureus</i> ATCC 29213 | 0.03-0.12 | — |
| <i>Staphylococcus aureus</i> ATCC 25923 | — | 29–37 |
| <i>Streptococcus pneumoniae</i> ATCC 49619 | 0.06-0.25 | 28–35 |
| <i>Enterococcus faecalis</i> ATCC 29212 | 2–8 | |
| <i>Escherichia coli</i> ATCC 25922 | 0.008-0.06 | 28–34 |
| <i>Haemophilus influenzae</i> ATCC 49766 | 0.03-0.12 | |
| <i>Haemophilus influenzae</i> | — | 20–28 |

| | | |
|--|-----------|-------|
| ATCC 49247 | | |
| <i>Pseudomonas aeruginosa</i> ATCC 27853 | 0.25-1 | 27–33 |
| <i>Bacteroides fragilis</i> [†] ATCC 25285 | 0.03–0.25 | |
| <i>Bacteroides thetaiotaomicron</i> [†] ATCC 29741 | 0.125-0.5 | |
| <i>Eubacterium lentum</i> [†] ATCC 43055 | 0.125-1 | |
| <i>Clostridium difficile</i> [†] ATCC 700057 | 0.5-4 | |

1. Using the Reference Agar Dilution procedure

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis:

Carcinogenesis studies have not been performed.

Mutagenesis:

Genetic toxicity studies were performed with meropenem using the bacterial reverse mutation test, the Chinese hamster ovary HGPRT assay, cultured human lymphocytes cytogenic assay, and the mouse micronucleus test. There was no evidence of mutagenic potential found in any of these tests.

Impairment of Fertility:

Reproductive studies were performed with meropenem in rats at doses up to 1000 mg/kg/day, and cynomolgus monkeys at doses up to 360 mg/kg/day (on the basis of AUC comparisons, approximately 1.8 times and 3.7 times, respectively, to the human exposure at the usual dose of 1 g every 8 hours). There was no reproductive toxicity seen.

14 CLINICAL STUDIES

14.1 Complicated Skin and Skin Structure Infections

Adult patients with complicated skin and skin structure infections including complicated cellulitis, complex abscesses, perirectal abscesses, and skin infections requiring intravenous antimicrobials, hospitalization, and surgical intervention were enrolled in a randomized, multi-center, international, double-blind trial. The study evaluated meropenem at doses of 500 mg administered intravenously every 8 hours and imipenem-cilastatin at doses of 500 mg administered intravenously every 8 hours. The study compared the clinical response between treatment groups in the clinically evaluable population at the follow-up visit (test-of-cure). The trial was conducted in the United States, South Africa, Canada, and Brazil. At enrollment, approximately 37% of the patients had underlying diabetes, 12% had underlying peripheral vascular disease and 67% had a surgical intervention. The study included 510 patients randomized to meropenem and 527 patients randomized to imipenem-cilastatin. Two hundred and sixty one (261) patients randomized to meropenem and 287 patients randomized to imipenem-cilastatin were clinically evaluable. The success rates in the clinically evaluable patients at the follow-up visit were 86% (225/261) in the meropenem arm and 83% (238/287) in imipenem-cilastatin arm.

The following table provides the results for the overall as well as subgroup comparisons in clinically evaluable population.

| Success Rate ¹ | | |
|---------------------------|---|---|
| Population | MERREM I.V. n ² /N ³ (%) | Imipenem-cilastatin n ² /N ³ (%) |
| Total | 225/261 (86) | 238/287 (83) |
| Diabetes mellitus | 83/97 (86) | 76/105 (72) |
| No diabetes mellitus | 142/164 (87) | 162/182 (89) |
| <65 years of age | 190/218 (87) | 205/241 (85) |
| ≥65 years of age | 35/43 (81) | 33/46 (72) |
| Men | 130/148 (88) | 137/172 (80) |
| Women | 95/113 (84) | 101/115 (88) |

1. Percent of satisfactory clinical response at follow-up evaluation.
2. n=number of patients with satisfactory response.
3. N=number of patients in the clinically evaluable population or respective subgroup within treatment groups.

The following clinical efficacy rates were obtained, per organism. The values represent the number of patients clinically cured/number of clinically evaluable patients at the post-treatment follow-up visit, with the percent cure in parentheses (Fully Evaluable analysis set).

| MICROORGANISMS ¹ | MERREM I.V. n ² /N ³ (%) ⁴ | Imipenem-cilastatin n ² /N ³ (%) ⁴ |
|---|--|--|
| Gram-positive aerobes | | |
| <i>Staphylococcus aureus</i> , methicillin susceptible | 82/88 (93) | 84/100 (84) |
| <i>Streptococcus pyogenes</i> (Group A) | 26/29 (90) | 28/32 (88) |
| <i>Streptococcus agalactiae</i> (Group B) | 12/17 (71) | 16/19 (84) |
| <i>Enterococcus faecalis</i> | 9/12 (75) | 14/20 (70) |
| <i>Streptococcus viridans</i> Group, nos | 11/12 (92) | 5/6 (83) |
| Gram-negative aerobes | | |
| <i>Escherichia coli</i> | 12/15 (80) | 15/21 (71) |
| <i>Pseudomonas aeruginosa</i> | 11/15 (73) | 13/15 (87) |
| <i>Proteus mirabilis</i> | 11/13 (85) | 6/7 (86) |
| Anaerobes | | |
| <i>Bacteroides fragilis</i> | 10/11 (91) | 9/10 (90) |
| <i>Peptostreptococcus</i> species | 10/13 (77) | 14/16 (88) |

1. Patients may have more than one pretreatment pathogen.
2. n=number of patients with satisfactory response.
3. N=number of patients in the clinically evaluable population or subgroup within treatment groups.
4. %= Percent of satisfactory clinical response at follow-up evaluation.

The proportion of patients who discontinued study treatment due to an adverse event was similar for both treatment groups (meropenem, 2.5% and imipenem-cilastatin, 2.7%).

14.2 Complicated Intra-Abdominal Infections

One controlled clinical study of complicated intra-abdominal infection was performed in the United States where meropenem was compared with clindamycin/tobramycin. Three controlled clinical studies of complicated intra-abdominal infections were performed in Europe; meropenem was compared with imipenem (two trials) and cefotaxime/metronidazole (one trial).

Using strict evaluability criteria and microbiologic eradication and clinical cures at follow-up which occurred 7 or more days after completion of therapy, the following presumptive microbiologic eradication/clinical cure rates and statistical findings were obtained:

| Treatment Arm | No. evaluable/ No. enrolled (%) | Microbiologic Eradication Rate | Clinical Cure Rate | Outcome |
|------------------------------|---------------------------------|--------------------------------|--------------------|-------------------------------------|
| meropenem | 146/516 (28%) | 98/146 (67%) | 101/146 (69%) | |
| | | | | |
| imipenem | 65/220 (30%) | 40/65 (62%) | 42/65 (65%) | Meropenem equivalent to control |
| | | | | |
| cefotaxime/ metronidazole | 26/85 (30%) | 22/26 (85%) | 22/26 (85%) | Meropenem not equivalent to control |
| | | | | |
| clindamycin/ tobramycin | 50/212 (24%) | 38/50 (76%) | 38/50 (76%) | Meropenem equivalent to control |

The finding that meropenem was not statistically equivalent to cefotaxime/metronidazole may have been due to uneven assignment of more seriously ill patients to the meropenem arm. Currently there is no additional information available to further interpret this observation.

14.3 Bacterial Meningitis

Four hundred forty-six patients (397 pediatric patients ≥ 3 months to < 17 years of age) were enrolled in 4 separate clinical trials and randomized to treatment with meropenem (n=225) at a dose of 40 mg/kg every 8 hours or a comparator drug, i.e., cefotaxime (n=187) or ceftriaxone (n=34), at the approved dosing regimens. A comparable number of patients were found to be clinically evaluable (ranging from 61-68%) and with a similar distribution of pathogens isolated on initial CSF culture.

Patients were defined as clinically not cured if any one of the following three criteria were met:

1. At the 5-7 week post-completion of therapy visit, the patient had any one of the following: moderate to severe motor, behavior or development deficits, hearing loss of >60 decibels in one or both ears, or blindness.
2. During therapy the patient's clinical status necessitated the addition of other antibiotics.
3. Either during or post-therapy, the patient developed a large subdural effusion needing surgical drainage, or a cerebral abscess, or a bacteriologic relapse.

Using the definition, the following efficacy rates were obtained, per organism. The values represent the number of patients clinically cured/number of clinically evaluable patients, with the percent cure in parentheses.

| MICROORGANISMS | MERREM I.V. | COMPARATOR |
|--|--------------|--------------|
| <i>S. pneumoniae</i> | 17/24 (71) | 19/30 (63) |
| <i>H. influenzae</i> (+) ¹ | 8/10 (80) | 6/6 (100) |
| <i>H. influenzae</i> (-/NT) ² | 44/59 (75) | 44/60 (73) |
| <i>N. meningitidis</i> | 30/35 (86) | 35/39 (90) |
| Total (including others) | 102/131 (78) | 108/140 (77) |

1. (+) β -lactamase-producing

2. (-/NT) non- β -lactamase-producing or not tested

Sequelae were the most common reason patients were assessed as clinically not cured.

Five patients were found to be bacteriologically not cured, 3 in the comparator group (1 relapse and 2 patients with cerebral abscesses) and 2 in the meropenem group (1 relapse and 1 with continued growth of *Pseudomonas aeruginosa*).

The adverse events seen were comparable between the two treatment groups both in type and frequency. The meropenem group did have a statistically higher number of patients with transient elevation of liver enzymes [see *Adverse Reactions* (6.1)]. Rates of seizure activity during therapy were comparable between patients with no CNS abnormalities who

received meropenem and those who received comparator agents. In the MERREM I.V. treated group, 12/15 patients with seizures had late onset seizures (defined as occurring on day 3 or later) versus 7/20 in the comparator arm.

With respect to hearing loss, 263 of the 271 evaluable patients had at least one hearing test performed post-therapy. The following table shows the degree of hearing loss between the meropenem-treated patients and the comparator-treated patients.

| Degree of Hearing Loss (in one or both ears) | Meropenem n = 128 | Comparator n = 135 |
|---|------------------------------|-------------------------------|
| No loss | 61% | 56% |
| 20-40 decibels | 20% | 24% |
| >40-60 decibels | 8% | 7% |
| >60 decibels | 9% | 10% |

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Ninth Edition*. CLSI document M07-A9, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition* CLSI document M02-A11, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-third Informational Supplement*, CLSI document M100-S23. CLSI document M100-S23, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2013
4. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard - Eight Edition*. CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087 USA, 2012
5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16:31-41.

16 HOW SUPPLIED/STORAGE AND HANDLING

MERREM I.V. is supplied in 20 mL and 30 mL injection vials containing sufficient meropenem to deliver 500 mg or 1 g for intravenous administration, respectively. The dry powder should be stored at controlled room temperature 20-25°C (68-77°F) [see USP].

500 mg Injection Vial (NDC 0310-0325-20)
1 g Injection Vial (NDC 0310-0321-30)

17 PATIENT COUNSELING INFORMATION

- Patients should be counseled that antibacterial drugs including MERREM I.V. should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When MERREM I.V. is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by MERREM I.V. or other antibacterial drugs in the future.
- Patients should be counseled that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible [see *Warnings and Precaution* (5.4)].
- Patients should be counseled to inform their physician if they are taking valproic acid or divalproex sodium. Valproic acid concentrations in the blood may drop below the therapeutic range upon co-administration with MERREM I.V. If treatment with MERREM I.V. is necessary and continued, alternative or supplemental anti-convulsant medication to prevent and/or treat seizures may be needed [see *Warnings and Precautions* (5.3)].
- Patients receiving MERREM I.V. on an outpatient basis may develop adverse events such as seizures, headaches and/or paresthesias that could interfere with mental alertness and/or cause motor impairment. Until it is reasonably well established that MERREM I.V. is well tolerated, patients should not operate machinery or motorized vehicles [see *Warnings and Precautions* (5.10)].

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Wilmington, DE 19850

Rev 11/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-706/S-034

SUMMARY REVIEW

Medical Officer Review of a Prior Approval Labeling Supplement

Merrem IV (meropenem for injection)

NDA-050706

Supplements S-32, (b) (4) S-34

Sponsor: AstraZeneca UK

BACKGROUND

Meropenem was initially approved in 1996, and is currently indicated for the treatment of complicated skin and skin structure infections (cSSSI), complicated intraabdominal infections (cIAI), and bacterial meningitis, with the following recommended doses:

- cSSSI: 10 mg/kg (max 500 mg) q8h
- cIAI: 20 mg/kg (max 1g) q8h
- Meningitis: 40 mg/kg (max 2g) q8h

In Supplement 31, submitted 20 June 2011, the Sponsor proposed a dosage adjustment for infections caused by *Pseudomonas aeruginosa*. The Sponsor provided justification for changes to the dosing recommendations (**1g IV q8h**), which would primarily impact the regimen for cSSSI. These changes were based on revised MIC interpretive criteria and probabilities of meropenem target attainment by Monte-Carlo simulation. The Sponsor agreed to defer these changes in order to discuss similar breakpoint issues in an AIDAC meeting, which was held 17 October 2013. In the meantime, the Division accepted the other proposed changes to the label ("Potential for Neuromotor Impairment").

In Supplement 32, submitted 28 February 2013, the Sponsor resubmitted their proposed wording for the dose recommendation for infections caused by *Pseudomonas aeruginosa*: "When treating infections (b) (4) caused by *Pseudomonas aeruginosa*, a dose of 1g every 8 hours is recommended. (b) (4)

There were no clinical study reports submitted with this labeling supplement.

(b) (4)

In Supplement 34, submitted 18 July 2013, the Sponsor submitted additional labeling changes based on information about transmission of meropenem in human breast milk.

SPONSOR'S PROPOSED LABELING CHANGES AND REVIEWER'S RECOMMENDATIONS:

The Sponsor recommends the following changes to Sections 2.1, 2.3, 2.6, 8.3 and 12.4 of the label. Additions are shown in blue underline and deletions are shown in ~~red strikethrough~~. The Reviewer Recommendations follow each recommended Sponsor change.

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

/s/

BENJAMIN D LORENZ

12/13/2013

Medical Officer/Acting Team Leader

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-706/S-034

CHEMISTRY REVIEW(S)

| | | | |
|---|---|---|--|
| CHEMIST'S REVIEW # 1 | | 1. ORGANIZATION HFD-520 | 2. NDA NUMBER 50-706/S-034 CBE-30 |
| 3. NAME AND ADDRESS OF APPLICANT (City and State) AstraZeneca UK Limited Alderley Park, Macclesfield, Cheshire, UK, SK10 4TG US Agent: Cynthia S. Dommissie 1800 Concord Pike P.O. Box 8355 Wilmington, DE, 19803-8355 | | Labeling supplement | |
| | | 4. AF NUMBER | |
| | | 5. SUPPLEMENT(S) NUMBER(S) DATE(S) Letter date 7/18/13 Receive date: 7/18/13 Goal date: 11/18/13 | |
| 6. NAME OF DRUG: Merrem I.V.®(meropenem for injection) | 7. NONPROPRIETARY NAME Meropenem | | |
| 8. SUPPLEMENT PROVIDES FOR: Updates to DOSAGE AND ADMINISTRATION section, Stability and Storage subsection (2.6), and USE IN SPECIFIC POPULATIONS section, Nursing Mothers subsection (8.3). | | 9. AMENDMENT(S), REPORT(S), ETC. NUMBER(S) DATE(S) | |
| 10. PHARMACOLOGICAL CATEGORY Anti infectious | 11. HOW DISPENSED RX <u>X</u> OTC | | 12. RELATED IND/NDA/DMF |
| 13. DOSAGE FORM(S) Injection | 14. POTENCY 500 mg and 1 g | | |
| 15. CHEMICAL NAME AND STRUCTURE See review text | | 16. RECORDS AND REPORTS CURRENT YES <input type="checkbox"/> NO REVIEWED YES <input type="checkbox"/> NO | |
| 17. COMMENTS: | | | |
| 18. CONCLUSIONS AND RECOMMENDATIONS: From CMC standpoint, this supplement is recommended for approval . cc: Orig. NDA 50-706/S-034 HFD-520/div. File doc # N:\NDA\50-706\S-034\Chem\11/12/2013. REV | | | |
| 19. REVIEWR NAME: Hossein S. Khorshidi | SIGNATURE | | DATE COMPLETED 11/12/2013 |

3 Pages Immediately Following Withheld - b(4)

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

/s/

NAVDEEP BHANDARI

12/06/2013

Entered on behalf of Hossein S. Khorshidi

THOMAS F OLIVER

12/06/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-706/S-034

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



NDA 050706/S-034

**ACKNOWLEDGEMENT --
CHANGES BEING EFFECTED SUPPLEMENT**

AstraZeneca Pharmaceuticals LP
Attention: Cynthia S. Dommissie, PharmD.
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Dommissie:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 050706
SUPPLEMENT NUMBER: S-034
PRODUCT NAME: MERREM I.V. (meropenem for injection)
DATE OF SUBMISSION: July 18, 2013
DATE OF RECEIPT: July 18, 2013

This “Changes Being Effected in 30 Days” supplemental application updates **DOSAGE AND ADMINISTRATION** section, **Stability and Storage** subsection (2.6), and **USE IN SPECIFIC POPULATIONS** section, **Nursing Mothers** subsection (8.3).

This application was filed on September 16, 2013, in accordance with 21 CFR 314.101(a). The goal date is January 18, 2014.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call Susmita Samanta, Safety Regulatory Project Manager at (301) 796-0803.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

SUSMITA SAMANTA

10/11/2013

Signing for Frances LeSane