CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

50-706 / S-018

Trade Name: Merrem

Generic Name: (meropenem)

Sponsor: AstraZeneca Pharmaceuticals LP

Approval Date: May 25, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-706 / S-018

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-706 / S-018

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-706/S-018

AstraZeneca Pharmaceuticals LP
Attention: Patricia Neall
Associate Director, Regulatory Affairs
1800 Concord Pike
P. O. Box 8355
Wilmington, Delaware 19803-8355

Dear Ms. Neall:

Please refer to your supplemental new drug application dated July 28, 2004, received July 28, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MERREM® (meropenem for injection) IV. This application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated September 22, October 20, December 15, 2004, February 4 and 16, April 15, and May 16, 2005.

This supplemental application provides for the use of meropenem, 500 mg IV every 8 hours, as treatment for patients with complicated skin and skin structure infections (cSSSI) due to *Staphylococcus aureus* (methicillin susceptible strains), *Streptococcus pyogenes, Streptococcus agalactiae,* viridans group streptococci, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli, Proteus mirabilis, Bacteroides fragilis,* and *Peptostreptococcus* species.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 50-706/S-018**". Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and

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

/s/

Janice Soreth
5/25/05 12:36:48 PM

effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application for pediatric patients of age less than 3 months. We note that you have fulfilled the pediatric study requirement for this application for pediatric patients aged ≥3 months through 17 years.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division, and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective and Ophthalmology Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-706 / S-018

APPROVED LABELING

MERREM® I.V.

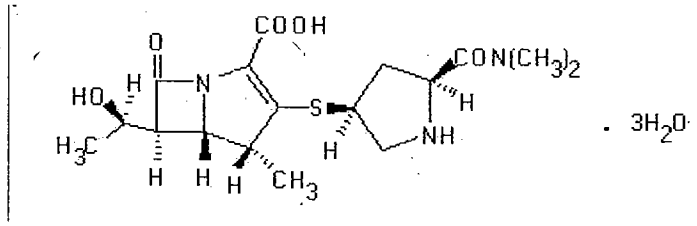
(meropenem for injection)

FOR INTRAVENOUS USE ONLY

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

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 (see **DOSAGE AND ADMINISTRATION; PREPARATION OF SOLUTION**), 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).

CLINICAL PHARMACOLOGY

At the end of a 30-minute intravenous infusion of a single dose of MERREM I.V. in normal volunteers, mean peak plasma concentrations are approximately 23 µg/mL (range 14-26) for the 500 mg dose and 49 µg/mL (range 39-58) for the 1 g dose. A 5-minute intravenous bolus injection of MERREM I.V. in normal volunteers results in mean peak plasma concentrations of approximately 45 µg/mL (range 18-65) for the 500 mg dose and 112 µg/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 µg/mL at 6 hours after administration.

In subjects with normal renal function, the elimination half-life of MERREM I.V. is approximately 1 hour. Approximately 70% of the intravenously administered dose is recovered as unchanged meropenem in the urine over 12 hours, after which little further urinary excretion is detectable. Urinary concentrations of meropenem in excess of 10 µg/mL are maintained for up to 5 hours after a 500 mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every 8 hours or 1 g administered every 6 hours in volunteers with normal renal function.

Plasma protein binding of meropenem is approximately 2%. There is one metabolite which is microbiologically inactive.

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 [µg/mL or µg/(g)]*	Range [µg/mL or µg/(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**	0.5	9	5.5	3.2-8.6
Skin	1.0	10	5.3	1.3-16.7
Interstitial fluid**	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***	8	1.1 (2 h)	0.2-2.8
	40 mg/kg****	5	3.3 (3 h)	0.9-6.5
CSF (uninflamed)	1.0	4	0.2 (2 h)	0.1-0.3

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

The pharmacokinetics of MERREM I.V. 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.

Pharmacokinetic studies with MERREM I.V. in patients with renal insufficiency have shown that the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment. (See **DOSAGE AND ADMINISTRATION - Use in Adults with Renal Impairment**.) A pharmacokinetic study with MERREM I.V. in elderly patients with renal insufficiency has shown a reduction in plasma clearance of meropenem that correlates with age-associated reduction in creatinine clearance.

Meropenem I.V. is hemodialyzable. However, there is no information on the usefulness of hemodialysis to treat overdosage. (See **OVERDOSAGE**.)

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

Microbiology

Meropenem is a broad-spectrum carbapenem antibiotic. It is active against Gram-positive and Gram-negative bacteria.

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 $\log_{10}$ 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 of most categories, both penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria.

Meropenem should not be used to treat methicillin-resistant staphylococci (MRSA).

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

Mechanism of Action

Meropenem exerts its action by penetrating bacterial cells readily and interfering with the synthesis of vital cell wall components, which leads to cell death.

Resistance

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 penicillin binding proteins (PBP), 3) increased expression of efflux pump components, and 4) production of antibiotic-destroying enzymes (carbapenemases, metallo-β-lactamases).

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

Lists of Microorganisms

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

Aerobic and facultative Gram-positive microorganisms

Enterococcus faecalis (excluding vancomycin-resistant isolates)

Staphylococcus aureus (β-lactamase and non-β-lactamase producing, methicillin-susceptible isolates only)

Streptococcus agalactiae

Streptococcus pneumoniae (penicillin-susceptible isolates only)

NOTE: Penicillin-resistant isolates had meropenem MIC_{90} values of 1 or 2 μg/mL, which is above the 0.12 μg/mL susceptible breakpoint for this species.

Streptococcus pyogenes

Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms

Escherichia coli
Haemophilus influenzae (β-lactamase and non-β-lactamase producing)

Klebsiella pneumoniae
Neisseria meningitidis
Pseudomonas aeruginosa
Proteus mirabilis

Anaerobic microorganisms

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 microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoints for meropenem. However, the safety and effectiveness of meropenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic and facultative Gram-positive microorganisms

Staphylococcus epidermidis (β-lactamase and non-β-lactamase-producing), methicillin-susceptible isolates only).

Aerobic and facultative Gram-negative microorganisms

Acinetobacter species
Aeromonas hydrophila
Campylobacter jejuni
Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Haemophilus influenzae
(ampicillin-resistant, non-β-lactamase-producing isolates
[BLNAR isolates)
Hafnia alvei
Klebsiella oxytoca
Moraxella catarrhalis
(β-lactamase and non-β-lactamase-producing isolates)
Morganella morganii
Pasteurella multocida
Proteus vulgaris
Salmonella species
Serratia marcescens
Shigella species
Yersinia enterocolitica

Anaerobic microorganisms

Bacteroides distasonis
Bacteroides ovatus
Eubacterium lentum
Fusobacterium species

Bacteroides uniformis	*Prevotella bivia*
Bacteroides ureolyticus	*Prevotella intermedia*
Bacteroides vulgatus	*Prevotella melaninogenica*
Clostridium difficile	*Porphyromonas asaccharolytica*
Clostridium perfringens	*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 procedure. Standardized procedures are based on a dilution method[1,3] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of meropenem powder. The MIC values should be interpreted according to the following 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. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10-µg of meropenem to test the susceptibility of microorganisms to meropenem. The disk diffusion interpretive criteria are provided in Table 2.

Streptococcus pneumoniae isolates should be tested using 1-µg/mL oxacillin disk. Isolates with oxacillin zone sizes of ≥ 20 mm are susceptible (MIC ≤ 0.06 µg/mL) to penicillin and can be considered susceptible to meropenem for approved indications, and meropenem need not be tested. A meropenem MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤19 mm. The disk test does not distinguish penicillin intermediate isolates (i.e., MIC's = 0.12-1.0 µg/mL) from isolates that are penicillin resistant (i.e., MICs ≥ 2 µg/mL). Viridans group streptococci should be tested for meropenem susceptibility using an MIC method. Reliable disk diffusion tests for meropenem do not yet exist for testing streptococci.

Anaerobic techniques:

For anaerobic bacteria, the susceptibility to meropenem as MICs can be determined by standardized test methods.[4] The MIC values obtained should be interpreted according to the criteria provided in Table 2.

Table 2. Susceptibility Interpretive Criteria for Meropenem

Susceptibility Test Result Interpretive Criteria

	Minimum Inhibitory Concentrations (μg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	S	I	R[a]	S	I	R[a]
Enterobacteriaceae, *Acinetobacter* spp. and *Pseudomonas aeruginosa*	≤ 4	8	≥ 16	≥ 16	14-15	≤ 13
Haemophilus influenzae	≤ 0.5	--	--	≥ 20	--	--
Staphylococcus aureus[b]	≤ 4	8	≥ 16	≥ 16	14-15	≤ 13
Streptococcus pneumoniae[c]	≤ 0.12	--	--			
Streptococcus agalactiae[c] and *Streptococcus pyogenes*[c]	≤ 0.5	--	--			
Anaerobes[d]	≤ 4	8	≥ 16			

[a] The current absence of data on resistant isolates precludes defining any category other than "Susceptible." If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

[b] Staphylococci that are resistant to methicillin/oxacillin must be considered resistant to meropenem.

[c] No Disk diffusion (zone diameter) interpretative criteria have been established for testing *Streptococcus pneumoniae*, *Streptococcus agalactiae*, and *Streptococcus pyogenes*. Use Dilution (MICs) techniques results.

[d] MIC 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.

No interpretative criteria have been established for testing enterococci and *Neisseria meningitidis*.

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 control microorganisms to control the technical aspects of the test procedures. 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 = µg/mL)	Disk Diffusion (Zone diameters in mm)
Staphylococcus aureus ATCC 29213	0.03-0.12	
Staphylococcus aureus ATCC 25923		29-37
Streptococcus pneumoniae ATCC 49619	0.06-0.25	28-35
Enterococcus faecalis ATCC 29212	2.0-8.0	
Escherichia coli ATCC 25922	0.008-0.06	28-34
Haemophilus influenzae ATCC 49766	0.03-0.12	
Haemophilus influenzae ATCC 49247		20-28
Pseudomonas aeruginosa ATCC 27853	0.25-1.0	27-33
Bacteroides fragilis[d] ATCC 25285	0.03-0.25	
Bacteroides thetaiotaomicron[d] ATCC 29741	0.125-0.5	
Eubacterium lentum[d] ATCC 43055	0.125-1	

[d] Using the Reference Agar Dilution procedure.

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 indicated as single agent therapy for the treatment of the following infections when caused by susceptible isolates of the designated microorganisms:

Skin and Skin Structure Infections

Complicated skin and skin structure infections due to *Staphylococcus aureus* (β-lactamase and non-β-lactamase producing, methicillin-susceptible isolates only), *Streptococcus pyogenes, Streptococcus agalactiae,* viridans group streptococci, *Enterococcus faecalis* (excluding vancomycin-resistant isolates), *Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Bacteroides fragilis* and *Peptostreptococcus* species.

Intra-abdominal Infections

Complicated appendicitis and peritonitis caused by viridans group streptococci, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides fragilis, B. thetaiotaomicron,* and *Peptostreptococcus* species.

Bacterial Meningitis (Pediatric patients ≥ 3 months only)

Bacterial meningitis caused by *Streptococcus pneumoniae*‡, *Haemophilus influenzae* (β-lactamase and non-β-lactamase-producing isolates), 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 **PRECAUTIONS - Pediatrics**, **ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION** sections.
Appropriate cultures should usually be performed before initiating antimicrobial treatment in order to isolate and identify the organisms causing infection and determine their susceptibility to MERREM I.V.

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

Antimicrobial therapy should be adjusted, if appropriate, once the results of culture(s) and antimicrobial susceptibility testing are known.

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.

WARNINGS

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.**

Seizures and other CNS adverse experiences have been reported during treatment with MERREM I.V. (See **PRECAUTIONS** and **ADVERSE REACTIONS**.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including meropenem, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General:

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.

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.

During clinical investigations, 2904 immunocompetent adult patients were treated for infections outside the CNS, 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 - Use in Adults with Renal Impairment**.)

Close adherence to the recommended dosage regimens is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant 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.

In patients with renal dysfunction, thrombocytopenia has been observed but no clinical bleeding reported. (See **DOSAGE AND ADMINISTRATION - Use in Adults with Renal Impairment**.)

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

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.

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.

Drug Interactions:

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem. This led to statistically significant increases in the elimination half-life (38%) and in the extent of systemic exposure (56%). Therefore, the coadministration of probenecid with meropenem is not recommended.

There is evidence that meropenem may reduce serum levels of valproic acid to subtherapeutic levels (therapeutic range considered to be 50 to 100 μg/mL total valproate).

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.

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.

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 **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION**, and **CLINICAL STUDIES** sections.)

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MERREM I.V. is administered to a nursing woman.

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.

A pharmacokinetic study with MERREM I.V. in elderly patients with renal insufficiency has shown a reduction in plasma clearance of meropenem that correlates with age-associated reduction in creatinine clearance. (See **DOSAGE AND ADMINISTRATION; Use in Adults with Renal Impairment**).

MERREM I.V. is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. 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.

Information For Patients:

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 (eg, 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.

ADVERSE REACTIONS

Adult Patients:

During clinical investigations, 2904 immunocompetent adult patients were treated for infections outside the CNS with MERREM I.V. (500 mg or 1000 mg q 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 clinical 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 adverse systemic clinical 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 (see **PRECAUTIONS**), nervousness, paresthesia, hallucinations, somnolence, anxiety, depression, asthenia

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).

Urinalysis: presence of red blood cells

Complicated Skin and Skin Structure Infection

In a study of complicated skin and skin structure infection, the type of clinical adverse reactions were similar to those listed above. The patients with the most common adverse events with an incidence of >5% 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 abnormalities seen in the pediatric-aged patients in both the pediatric and the meningitis studies are similar to those reported in adult patients.

There is no experience in pediatric patients with renal impairment.

Post-marketing Experience:

Worldwide post-marketing adverse events not previously listed in the 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. Skin – toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, and erythema multiform.

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.

No specific information is available for the treatment of MERREM I.V. overdosage. In the event of an overdose, MERREM I.V. should be discontinued and general supportive treatment given until 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.

CLINICAL STUDIES

Skin and Skin Structure

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*		
Population	MERREM I.V. n/N (%)	Imipenem-cilastatin n/N (%)
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)

* Percent of satisfactory clinical response at follow-up evaluation.

n=number of patients with satisfactory response.

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

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

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%).

Intra-abdominal:

One controlled clinical study of complicated intra-abdominal infection was performed in the United States where meropenem was compared to clindamycin/tobramycin. Three controlled clinical studies of complicated intra-abdominal infections were performed in Europe; meropenem was compared to 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 notequivalent 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.

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 q 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
S. pneumoniae	17/24 (71)	19/30 (63)
H. influenzae (+)	8/10 (80)	6/6 (100)
H. influenzae (-/NT)	44/59 (75)	44/60 (73)
N. meningitidis	30/35 (86)	35/39 (90)
Total (including others)	102/131 (78)	108/140 (77)

(+) β-lactamase-producing; (-/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**). 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%

DOSAGE AND ADMINISTRATION

Adults:

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. 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.

Use in Adults with Renal Impairment:

Dosage should be reduced in patients with creatinine clearance less than 51 mL/min. (see dosing table below).

Recommended MERREM I.V. Dosage Schedule for Adults With Impaired Renal Function

Creatinine Clearance (mL/min)	Dose (dependent on type of infection)	Dosing Interval
≥ 51	Recommended dose (500 mg cSSSI 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

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

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

There is no experience with peritoneal dialysis.

Use in Adults With Hepatic Insufficiency:

No dosage adjustment is necessary in patients with impaired hepatic function.

Use in Elderly Patients:

No dosage adjustment is required for elderly patients with creatinine clearance values above 50 mL/min.

Use in Pediatric Patients:

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.

Recommended MERREM I.V. Dosage Schedule for Pediatrics 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

There is no experience in pediatric patients with renal impairment.

PREPARATION OF SOLUTION

For Intravenous Bolus Administration:

Constitute injection vials (500 mg and 1g) 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 1g) may be directly constituted with a compatible infusion fluid (See **COMPATIBILITY AND STABILITY.**) 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 **COMPATIBILITY AND STABILITY.**)

WARNING: Do not use flexible container in series connections.

COMPATIBILITY AND STABILITY

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.

Freshly prepared solutions of MERREM I.V. should be used whenever possible. However, constituted solutions of MERREM I.V. maintain satisfactory potency at controlled room temperature 15-25°C (59-77°F) or under refrigeration at 4°C (39°F) as 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 2 hours at controlled room temperature 15-25°C (59-77°F) or for up to 12 hours at 4°C (39°F).

Intravenous Infusion Administration:

Stability in Infusion Vials: MERREM I.V. infusion vials constituted with Sodium Chloride Injection 0.9% (MERREM I.V. concentrations ranging from 2.5 to 50 mg/mL) are stable for up to 2 hours at controlled room temperature 15-25°C (59-77°F) or for up to 18 hours at 4°C (39°F). Infusion vials of MERREM I.V. constituted with Dextrose Injection 5% (MERREM I.V. concentrations ranging from 2.5 to 50 mg/mL) are stable for up to 1 hour at controlled room temperature 15-25°C (59-77°F) or for up to 8 hours at 4°C (39°F).

Stability in Plastic I.V. Bags: Solutions prepared for infusion (MERREM I.V. concentrations ranging from 1 to 20 mg/mL) may be stored in plastic intravenous bags with diluents as shown below:

	Number of Hours at Controlled Room Temperature 15-25°C (59-77°F)	Number of Hours stable at 4°C (39°F)
Sodium Chloride Injection 0.9%	4	24
Dextrose Injection 5.0%	1	4
Dextrose Injection 10.0%	1	2
Dextrose and Sodium Chloride Injection 5.0%/0.9%	1	2
Dextrose and Sodium Chloride Injection 5.0%/0.2%	1	4
Potassium Chloride in Dextrose Injection 0.15%/5.0%	1	6
Sodium Bicarbonate in Dextrose Injection 0.02%/5.0%	1	6
Dextrose Injection 5.0% in Normosol®-M	1	8
Dextrose Injection 5.0% in Ringers Lactate Injection	1	4
Dextrose and Sodium Chloride Injection 2.5%/0.45%	3	12
Mannitol Injection 2.5%	2	16
Ringers Injection	4	24
Ringers Lactate Injection	4	12
Sodium Lactate Injection 1/6 N	2	24

Sodium Bicarbonate Injection 5.0% 1 4

Stability in Baxter Minibag Plus: Solutions of MERREM I.V. (MERREM I.V. concentrations ranging from 2.5 to 20 mg/mL) in Baxter Minibag Plus bags with Sodium Chloride Injection 0.9% may be stored for up to 4 hours at controlled room temperatures 15-25°C (59-77°F) or for up to 24 hours at 4°C (39°F). Solutions of MERREM I.V. (MERREM I.V. concentrations ranging from 2.5 to 20 mg/mL) in Baxter Minibag Plus bags with Dextrose Injection 5.0% may be stored up to 1 hour at controlled room temperatures 15-25°C (59-77°F) or for up to 6 hours at 4°C (39°F).

Stability in Plastic Syringes, Tubing and Intravenous Infusion Sets: Solutions of MERREM I.V. (MERREM I.V. concentrations ranging from 1 to 20 mg/mL) in Water for Injection or Sodium Chloride Injection 0.9% (for up to 4 hours) or in Dextrose Injection 5.0% (for up to 2 hours) at controlled room temperatures 15-25°C (59-77°F) are stable in plastic tubing and volume control devices of common intravenous infusion sets.

Solutions of MERREM I.V. (MERREM I.V. concentrations ranging from 1 to 20 mg/mL) in Water for Injection or Sodium Chloride Injection 0.9% (for up to 48 hours) or in Dextrose Injection 5% (for up to 6 hours) are stable at 4°C (39°F) in plastic syringes.

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

HOW SUPPLIED

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)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-706 / S-018

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	NDA
Submission Number	50-706
Submission Code	S-018
Letter Date	July 28, 2004
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Reviewer Name	Thomas Smith, M.D.
Review Completion Date	March 25, 2005
Established Name	Meropenem
Trade Name	MERREM®
Therapeutic Class	Carbapenem antimicrobial
Applicant	AstraZeneca Pharmaceuticals LP
Priority Designation	S
Formulation	Intravenous
Dosing Regimen	500 mg q8h
Indication	Complicated skin and skin structure infections
Intended Population	Adults and pediatric patients ≥3 months of age

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The applicant has submitted one adequate and well-controlled trial demonstrating that meropenem 500 mg iv q8h is noninferior to imipenem-cilastatin 500 mg iv q8h for the treatment of complicated skin and skin structure infections (SSSI) due to susceptible strains of *Staphylococcus aureus* (methicillin susceptible strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, viridans streptococci, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species. The overall safety profile for meropenem in this trial was similar to that of imipenem-cilastatin and is consistent with the current meropenem labeling. The most frequently reported drug-related adverse event in patients receiving meropenem was diarrhea.

The efficacy findings from this clinical trial are supported by a pharmacokinetic study in healthy subjects which demonstrated that the penetration of a 500 mg dose of meropenem into skin blister fluid is likely to be adequate for the treatment of complicated SSSI due to susceptible strains of the designated microorganisms.

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

1.2 Recommendation on Postmarketing Actions

Meropenem was approved in the United States in 1996 for other indications, and no changes in current postmarketing requirements are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Meropenem is a broad-spectrum carbapenem antimicrobial for intravenous administration. It is approved in the United States for use as single-agent therapy for the treatment of complicated appendicitis and peritonitis in adults and pediatric patients ≥3 months of age and bacterial meningitis in pediatric patients ≥3 months of age, when caused by susceptible pathogens. The present efficacy supplement seeks to add an indication for complicated SSSI.

The applicant performed a single efficacy and safety trial in hospitalized adults with complicated SSSI; this trial enrolled 1076 patients, with 535 patients randomized to receive meropenem. The safety database includes 511 patients who received meropenem for a mean duration of 5.8 days (range 1 to 17 days).

The applicant also performed a pharmacokinetic study of the penetration of meropenem into skin blister fluid. Meropenem levels were measured in plasma and in cantharidin-induced skin blisters in 10 healthy adult subjects following three 500 mg infusions of meropenem.

1.3.2 Efficacy

Study 3591IL/0079 was a multicenter, randomized, double-blind trial which compared meropenem 500 mg iv q8h with imipenem-cilastatin 500 mg iv q8h for the treatment of complicated SSSI in hospitalized adult patients. The primary endpoint for this trial was clinical outcome at the post-treatment follow-up visit 7 to 14 days after completion of therapy; analyses of the clinically evaluable and modified intent to treat (MITT) populations were considered co-primary. The major secondary endpoints were clinical outcomes at the post-treatment follow-up visit in the intent to treat (ITT), microbiologic ITT, microbiologic MITT, and fully evaluable populations; and microbiologic and pretreatment pathogen outcomes at follow-up in the microbiologically evaluable populations.

This study enrolled 1076 patients, with 535 patients randomized to receive meropenem and 541 randomized to receive imipenem-cilastatin. There were minor discrepancies in the applicant's and medical officer's evaluability determinations, but these did not affect interpretation of the study outcomes. In the medical officer's clinically evaluable population, cure rates at follow-up were 85.4% (217/254) for meropenem and 81.4% (227/279) for imipenem-cilastatin; the treatment difference (meropenem minus imipenem-cilastatin) was 4.0% (95% confidence interval (CI), -2.2, 10.4). In the applicant's clinically evaluable population, cure rates at follow-up were 86.2% (225/261) for meropenem and 82.9% (238/287) for imipenem-cilastatin; the treatment difference was 3.3% (95% CI, -2.8, 9.3). In the medical officer's MITT population, cure rates at follow-up were 72.4% (234/323) for meropenem and 73.5% (253/344) for imipenem-cilastatin; the treatment difference was -1.1% (95% CI, -7.8, 5.6). In the applicant's MITT population, cure rates at follow-up were 73.1% (244/334) for meropenem and 74.9% (268/358) for imipenem-cilastatin; the treatment difference was -1.8% (95% CI, -8.4, 4.7). For all analyses, the lower limits of the 95% CIs around the treatment differences were greater than -10%. The secondary endpoint analyses were generally consistent with the primary endpoint analyses.

Charles Bonapace, Pharm.D., reviewed the skin blister pharmacokinetic study report and had the following conclusions and comments. The mean percent penetration of meropenem into skin blister fluid was 66.8%, using the skin blister fluid/plasma AUC_{0-t} ratio. The protein binding of meropenem in skin blister fluid is expected to be similar to that in plasma, approximately 2%. This study did not evaluate the effect of infection on the penetration of meropenem into interstitial fluid. If the penetration of meropenem is similar between healthy subjects and patients with infection, the results suggest that meropenem 500 mg iv q8h may be effective in the treatment of complicated SSSI. This study report was acceptable from a clinical pharmacology standpoint.

In Study 3591IL/0079, the applicant demonstrated that meropenem 500 mg iv q8h is noninferior to imipenem-cilastatin 500 mg iv q8h for the treatment of complicated SSSI. The results of this

study, together with the findings of the skin blister pharmacokinetic study, support the approval of meropenem for the treatment of complicated SSSI due to *Staphylococcus aureus* (methicillin susceptible strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, viridans streptococci, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species.

1.3.3 Safety

In Study 3591IL/0079, 511 patients received at least one dose of meropenem (mean 5.8 days, range 1 to 17 days), and 526 patients received at least one dose of imipenem-cilastatin (mean 6.0 days, range 1 to 20 days). The dose of meropenem in this study, 500 mg q8h, is one-half the dose in the approved labeling for intraabdominal infections.

Adverse events (AEs) were recorded daily during study drug administration and at the post-treatment follow-up visit. Laboratory testing of hematologic status and renal and hepatic function was performed at study entry, during study therapy as needed, at the end of study therapy, and at follow-up as needed.

The most frequently reported AEs in patients receiving meropenem were headache, nausea, constipation, and diarrhea. The most frequently reported drug-related AE in patients receiving meropenem was diarrhea. The overall safety profile for meropenem in this study was similar to that of imipenem-cilastatin and is consistent with the current meropenem labeling.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen of meropenem, 500 mg iv q8h for adult patients, is effective for the treatment of complicated SSSI due to susceptible strains of the designated microorganisms. The appropriate dosing regimen for the treatment of pediatric patients ≥3 months of age with complicated SSSI is 10 mg/kg iv q8h.

1.3.5 Drug-Drug Interactions

No new information regarding drug-drug interactions was identified.

1.3.6 Special Populations

The applicant previously submitted a pediatric assessment which proposed a dose of 10 mg/kg q8h for complicated SSSI in pediatric patients ≥3 months of age. This dose is supported by results from the pharmacokinetic and clinical trials included in the present efficacy supplement, along with previously submitted data from studies of meropenem in pediatric patients. This reviewer recommends granting the applicant a partial waiver of the requirement to submit an assessment for pediatric patients <3 months of age on the grounds that the necessary studies are impracticable because the incidence of complicated SSSI in this population is so small and the patients are geographically dispersed.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Meropenem (MERREM®) is a broad-spectrum carbapenem antimicrobial for intravenous (iv) administration. The present supplemental New Drug Application is for the proposed indication of complicated skin and skin structure infections (SSSI), with a proposed dose of 500 mg iv q8h for adults.

2.2 Currently Available Treatment for Indication

Currently available treatments for the indication of complicated SSSI include ertapenem, levofloxacin, piperacillin/tazobactam, linezolid, daptomycin, and quinupristin/dalfopristin. Of these agents, only ertapenem and levofloxacin are approved for complicated SSSI due to gram-positive and gram-negative bacteria; the other agents are approved for complicated SSSI due to selected gram-positive bacteria only. In addition, a number of other parenteral antimicrobials, including imipenem-cilastatin, several cephalosporins, two β-lactam/β-lactamase inhibitor combinations, aztreonam, and ciprofloxacin were approved for the treatment of SSSI before the "complicated" category came into use.

2.3 Availability of Proposed Active Ingredient in the United States

Meropenem is approved in the United States for use as single-agent therapy for the treatment of complicated appendicitis and peritonitis in adults and children and bacterial meningitis in infants and children when caused by susceptible pathogens. The dose for complicated intraabdominal infections is 1 g q8h for adults and 20 mg/kg q8h for children; the dose for meningitis in infants and children is 40 mg/kg q8h (maximum 2 g q8h).

2.5 Presubmission Regulatory Activity

AstraZeneca submitted the original NDA for meropenem in 1993 for several indications, including uncomplicated and complicated SSSI. In 1994, the FDA issued a not approvable letter to AstraZeneca for all requested indications. AstraZeneca withdrew the NDA and resubmitted it in 1995 for several indications, including uncomplicated and complicated SSSI. In 1996, the FDA issued an approval letter for complicated intraabdominal infections and for bacterial meningitis in pediatric patients (≥3 months); the other indications were not approvable. In each submission, meropenem was not approved for the SSSI indication because of an insufficient number of evaluable patients.

The following are important dates in the regulatory history of the current submission:

August 21, 2000: AstraZeneca submitted a draft clinical trial protocol (3591IL/0079) for the complicated SSSI indication.

February 8, 2001: AstraZeneca submitted protocol 3591IL/0079 (IND 33,016; N-381).

December 19, 2001: AstraZeneca submitted a skin blister pharmacokinetic (pk) protocol, 3591IL/0091 (IND 33,016; N-412).

May 3, 2002: FDA stated that satisfactory results from clinical study 3591IL/0079 and skin blister pk study 3591IL/0091 would support addition of the complicated SSSI indication to the product label.

August 12, 2003: AstraZeneca submitted the pediatric plan for the complicated SSSI sNDA.

August 19, 2003: AstraZeneca submitted the skin blister pk study report (IND 33,016; N-458).

November 7, 2003: AstraZeneca submitted the pre-sNDA meeting briefing package.

February 19, 2004: AstraZeneca and FDA held a pre-sNDA teleconference.

July 28, 2004: AstraZeneca submitted the complicated SSSI sNDA (NDA 50-706; S-018).

2.6 Other Relevant Background Information

Meropenem is approved for use for various indications in over 80 countries.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This submission contains data from a phase 1 skin blister pk study (3591IL/0091) and a phase 3 clinical study in patients with complicated SSSI (3591IL/0079):

Study 3591IL/0091: "An Open-label Study to Determine the Concentration of Meropenem in Plasma and Cantharidin-induced Skin Blister Fluid Following Repeated Intravenous Infusion of Meropenem 500 mg Every 8 Hours in Healthy Males"

Study 3591IL/0079: "A Multicenter, Randomized, Double-blind, Comparative Trial of Intravenous MERREM™ (meropenem, ICI 194,660) vs PRIMAXIN® I.V. (imipenem-cilastatin) in the Treatment of Hospitalized Subjects with Complicated Skin and Skin Structure Infections"

4.2 Tables of Clinical Studies

Table 1 summarizes the submitted trials.

Table 1. Listing of Clinical Trials

Study Number	Population	Test Drugs	Enrollment
Pharmacokinetics			
3591IL/0091	Healthy subjects	Meropenem 500 mg q8h (3 doses)	10
Complicated Skin and Skin Structure Infections			
3591IL/0079	Hospitalized patients	Meropenem 500 mg q8h Imipenem-cilastatin 500 mg q8h	535 Meropenem 541 Imipenem-cilastatin

Adapted from Module 5, Table 5.2-1

4.3 Review Strategy

Detailed reviews of the data from the complicated SSSI trial are presented in the integrated reviews of efficacy (section 6) and safety (section 7). The phase 1 pharmacokinetics trial was reviewed in detail by Charles Bonapace, Pharm.D. His findings are summarized below in section 5.

4.4 Data Quality and Integrity

This medical officer performed a blinded review of a random sample of 10% of the case report forms (CRFs) from the complicated SSSI trial to verify the accuracy of the transcription of data from the CRFs to the database and to check for agreement with the applicant's evaluability and outcome determinations. The CRF review is discussed in detail in section 6.

4.5 Compliance with Good Clinical Practices

For the studies included in this sNDA, the applicant stated that institutional review board approval was obtained for each center, that the studies were conducted according to ethical principles originating in the Declaration of Helsinki and consistent with International Conference on Harmonisation good clinical practice guidance, and that informed consent was obtained from all patients or subjects before the start of any study procedures.

4.6 Financial Disclosures

The applicant submitted Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) stating that it had not entered into any financial arrangement with the listed clinical investigators in which compensation to the investigator could be affected by the outcome of the study. The applicant also reported that there were no disclosable financial interests for any of the responding principal or site investigators; one subinvestigator did not respond "after several telephone contacts".

Comment: This reviewer considers the disclosures to be acceptable.

5 CLINICAL PHARMACOLOGY

Charles Bonapace, Pharm.D., reviewed the skin blister pk study report and had the following conclusions and comments. The mean percent penetration of meropenem into skin blister fluid was 66.8%, using the skin blister fluid/plasma AUC_{0-t} ratio. The protein binding of meropenem in skin blister fluid is expected to be similar to that in plasma, approximately 2%. This study did not evaluate the effect of infection on the penetration of meropenem into interstitial fluid. If the penetration of meropenem is similar between healthy subjects and patients with infection, the results suggest that meropenem 500 mg iv q8h may be effective in the treatment of complicated SSSI. This study report was acceptable from a clinical pharmacology standpoint. Please refer to Dr. Bonapace's review for further details.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Complicated Skin and Skin Structure Infections

The applicant proposes the following labeling claim for the complicated SSSI indication:

> MERREM I.V. is indicated as single agent therapy for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:
>
> **Skin and Skin Structure infections**
> Complicated skin and skin structure infections due to *Staphylococcus aureus* (methicillin susceptible strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, viridans group streptococci, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species.

6.1.1 Methods

The applicant performed one clinical efficacy trial to support the complicated SSSI indication. Study 3591IL/0079 was a multicenter, randomized, double-blind trial intended to demonstrate the noninferiority of meropenem to the approved comparator imipenem-cilastatin in the treatment of hospitalized patients with complicated SSSI. The final protocol was dated 11/6/00 and submitted to the Agency 2/8/01. The first patient was enrolled 3/28/01, and the final patient completed the study 12/10/03. This trial is reviewed in detail in the sections that follow.

6.1.2 General Discussion of Endpoints

The primary endpoint for this trial was clinical outcome at the post-treatment follow-up visit 7 to 14 days after completion of therapy; analyses of the clinically evaluable and modified intent to treat (MITT) populations were considered co-primary. The major secondary endpoints were clinical outcomes at the post-treatment follow-up visit in the intent to treat (ITT), microbiologic

ITT, microbiologic MITT, and fully evaluable populations; and microbiologic and pretreatment pathogen outcomes at follow-up in the microbiologically evaluable populations.

Comment: The choice of primary endpoint is based on recommendations in the FDA draft guidance on uncomplicated and complicated SSSI. This document emphasizes analyses of the per protocol populations but also states that ITT analyses should be performed. The FDA review team recommended that the MITT analysis in this study be made co-primary, and the applicant agreed.

6.1.3 Study Design

6.1.3.1 Population

Inclusion Criteria

This study included patients 13 years of age or older who had clinical evidence of complicated SSSI requiring hospitalization and parenteral therapy. Complicated SSSI was defined as follows:

1. Complicated cellulitis: cellulitis with evidence of fever (≥38°C) or leukocytosis (WBC >10,000/mm^3) and at least one of the following:
    a. Underlying diabetes mellitus
    b. Requirement for surgical intervention including incision and drainage, debridement, or other significant intervention
    c. Evidence of deeper soft tissue involvement, including the presence of vesicles, bullae, tissue necrosis, fluctuance, exudate, drainage, or lymphangitis
    d. Bacteremia with an expected pathogen
    e. Involvement of skin in the perineal or perirectal area
2. Complex abscess: abscess requiring significant surgical intervention such as incision and drainage, excision, or debridement
3. Perirectal abscess
4. Wound infection: infection of surgical or traumatic wound with evidence of fever (≥38°C) or leukocytosis (WBC >10,000/mm^3) and requiring significant surgical intervention
5. Infected diabetic or ischemic ulcer: persistent open lower extremity wound in a patient with diabetes mellitus or arterial or venous peripheral vascular disease and evidence of acute superimposed bacterial infection, including purulent drainage, signs of local inflammation in adjacent nonulcerated tissue, and fever (≥38°C) or leukocytosis (WBC >10,000/mm^3), requiring significant surgical intervention
6. Other significant bacterial SSSI requiring surgical intervention

Within 72 hours before enrollment, an appropriate culture specimen must have been obtained. Appropriate specimens included a leading edge aspiration culture from patients with complicated cellulitis and biopsy, needle aspiration, surgically obtained specimen, or deep swab from patients with other complicated SSSI. Surface swabs of open wounds were unacceptable. Blood cultures

were to be obtained from all patients. All pretherapy pathogens had to be susceptible to meropenem, imipenem-cilastatin, and any subsequent oral therapy.

Patients could be enrolled before culture results were available. Patients who received more than 24 hours of antimicrobial therapy in the preceding 14 days could remain in the study only if a primary site culture or blood culture demonstrated persistence of a pathogen. Patients who had received less than 24 hours of antimicrobial therapy before enrollment could remain in the study even if the entry culture was negative. For all patients, no antibiotic therapy was allowed between the time of specimen collection and administration of study therapy.

Exclusion Criteria

Noteworthy exclusion criteria were:

1. Clinical or radiographic evidence of osteomyelitis
2. Another focus of infection requiring antibiotics that would interfere with evaluation of responses to study drugs
3. Severe peripheral vascular disease likely to require amputation
4. Cystic fibrosis or acquired immune deficiency syndrome
5. Decubitis ulcers of the hips, presacral area, or extremities
6. Necrotizing fasciitis
7. Infected prosthetic materials (e.g., central venous or dialysis catheter tunnel infections)
8. Leukopenia (WBC $<1000/mm^3$)

6.1.3.2 Study Procedures

Study Treatments

Patients were randomized to receive one of the following study therapies:

- Meropenem, 500 mg iv q8h
- Imipenem-cilastatin, 500 mg iv q8h

Comment: The labeled dose of imipenem-cilastatin for infections of moderate severity due to fully susceptible organisms is 500 mg administered either q6h or q8h. The q8h interval was chosen for this study to maintain blinding.

For patients with renal impairment, the dose and/or dosing interval was modified based on creatinine clearance as recommended in the respective product labels. Dosing adjustments were made for meropenem recipients with creatinine clearance $\leq$50 mL/min and for imipenem-cilastatin recipients with creatinine clearance $\leq$70 mL/min.

Treatment assignments were based on a randomization schedule provided to the hospital pharmacies by [redacted], an AstraZeneca contractor. The pharmacies prepared blinded infusion bags for administration to patients.

All patients were required to receive a minimum of 72 hours of iv study drug therapy. The duration of therapy was dependent on patient clinical response. A switch to oral antimicrobial therapy was permitted for patients meeting specified clinical and laboratory criteria. The choice of oral therapy was based on susceptibility of the documented or most likely infecting organisms. Maximum allowable therapy was 14 days for iv study drug and 21 days for combined iv-oral therapy.

No other concurrent systemic antibacterial therapy was permitted. Oral vancomycin was permitted for treatment of suspected or confirmed *Clostridium difficile* pseudomembranous colitis.

Surgical interventions for the complicated SSSI were permitted from 72 hours before to 48 hours after initiation of study therapy. Interventions more than 48 hours after initiation of study therapy were permitted if they were part of standard wound care, such as wound closure or removal of necrotic tissue. Persistent infections necessitating a second surgical intervention after at least 48 hours of study therapy were considered treatment failures.

The following adjunctive therapies were permitted:

- Daily dressing changes, including irrigation with povidone-iodine, saline, sodium hypochlorite, or neomycin sulfate-polymyxin B sulfate solution
- Local daily debridement at bedside
- Skin grafting or wound closure
- Whirlpool therapy
- Hyperbaric oxygen chamber
- Vacuum assisted closure system

If other adjunctive therapy was required after at least 48 hours of study drug therapy, the patient was discontinued and considered a treatment failure.

Study Evaluations

Pretherapy

- Collection of general patient information
- Description of signs and symptoms of infected area
- Physical examination
- Culture specimen from infected area
- Blood cultures
- Clinical laboratory tests (chemistry, hematology)
- Pregnancy test (if female of childbearing potential)

During therapy

- Daily clinical assessment
- Follow-up laboratory testing as needed

End of therapy (and before switch to oral therapy, if applicable)

- Clinical assessment
- Clinical response assessment
- Microbiologic response assessment
- Clinical laboratory tests

Posttherapy (7 to 14 days following completion of all antimicrobial therapy)

- Clinical assessment
- Clinical response assessment
- Microbiologic response assessment
- Follow-up laboratory testing as needed

The primary endpoint, clinical response at the posttherapy follow-up visit, was assessed by the investigator to be cure, failure, or relapse. For an outcome of cure, all signs and symptoms of the SSSI had to be resolved or improved to the extent that no further antimicrobial therapy was needed. The total duration of antimicrobial therapy could not exceed 14 days of iv therapy or 21 days of combined iv-oral therapy.

Clinical response was also assessed at the end of therapy visit. Possible responses were cure, improved, or failure.

Microbiologic response was assessed at the end of therapy and posttherapy follow-up visits for patients who had pretreatment pathogens isolated. Patients with documented eradication, presumed eradication, or colonization (growth of an organism that was not the original pathogen or growth of normal skin flora from a patient with a satisfactory clinical response) were considered to have had satisfactory microbiologic responses.

Pretreatment pathogen response was also determined at the end of therapy and follow-up visits. Satisfactory responses were documented or presumed eradication.

6.1.3.3 Statistical Considerations

The co-primary efficacy analyses were performed using clinical outcomes at follow-up in the clinically evaluable and MITT analysis sets. The clinically evaluable analysis set was the subset of the MITT set who satisfactorily completed the protocol (i.e., met inclusion and exclusion criteria, received adequate study therapy, and had appropriate follow-up). The MITT analysis set was the subset of the ITT set who met all inclusion and exclusion criteria.

> *Comment: Modification of the ITT analysis set was necessary because a substantial number of enrolled patients had to be discontinued from the study because of failure to fulfill inclusion or exclusion criteria. For example, the presence of a pathogen in a pretreated patient, the susceptibility of pathogens, and the presence of osteomyelitis could not always be determined at the time of enrollment into the study.*

Analyses were also performed of the ITT analysis set and of ITT, MITT, and clinically evaluable subsets having pathogens identified at baseline (microbiologic ITT, microbiologic MITT, and fully evaluable sets).

Noninferiority of meropenem to imipenem-cilastatin was determined if the lower bound of the two-sided 95% confidence interval (CI) of the difference in proportion of satisfactory clinical outcomes (meropenem minus imipenem-cilastatin) at the follow-up visit in the clinically evaluable analysis set was greater than -10% using the asymptotic normal approximation to the binomial distribution, without continuity correction. The MITT population was expected to have a lower response rate than the clinically evaluable population, and the study was not powered to meet a noninferiority criterion of -10% in the MITT population.

> *Comment: The division agreed that it was not necessary for the MITT analysis to achieve the -10% criterion as long as this analysis was otherwise consistent with the analysis of the clinically evaluable population.*

The applicant performed subgroup analyses based on primary diagnosis, need for renal dose adjustment, surgical intervention, age, gender, and race.

Because of the potential compromise of blinding in patients with renal dose adjustments and the lower than expected evaluability rates, recalculation of the sample size was required while the study was in progress. The applicant calculated that approximately 1000 patients would need to be enrolled to provide 201 clinically evaluable patients in each group, using an estimated response rate of 85% for each drug, noninferiority criterion of -10%, a two-sided 95% CI approach, power of 80%, and corrected evaluability rate of 55%. This calculation also accounted for the need to replace patients whose renal dose adjustments could compromise the study blind (approximately 20% of enrollees). The revised calculations were performed based on blinded review of incoming data.

> *Comment: The applicant discussed these issues with the division while the protocol was proceeding, and the division agreed to accept the revised sample size.*

6.1.3.4 Protocol Amendments and Changes in Analysis Plans

There were three protocol amendments. The first amendment (dated 7/7/01, submitted to FDA 2/7/02) placed limits on the allowable duration of antimicrobial therapy, clarified the disease definitions, and modified the exclusion criteria. The second amendment (dated 6/12/02, submitted to FDA 7/18/02) increased the number of participating centers to include international sites, expanded the case definition of cellulitis, modified the conditions under which patients who received prior therapy could participate, modified the allowable adjunctive therapies, and increased patient enrollment to account for the potential compromise of blinding in patients with renal dose adjustments. The third amendment (dated 2/25/03, submitted to FDA 3/31/03) increased patient enrollment to account for a decrease from the expected evaluability rate.

Comment: The second protocol amendment expanded the case definition of cellulitis to include patients with underlying conditions such as obesity, peripheral edema, malnutrition, and substance abuse. The supporting documentation submitted by the applicant was inadequate to justify the proposed expanded definition, and the applicant was informed that, in the absence of other factors defined in the FDA draft guidance on uncomplicated and complicated SSSI, such patients would be considered to have uncomplicated cellulitis. The applicant and the division subsequently agreed on the definition of complicated cellulitis stated in the inclusion criteria above.

6.1.4 Efficacy Findings

6.1.4.1 Demographics and Baseline Characteristics

One thousand seventy-six patients were randomized to receive one of the study therapies: 535 to receive meropenem and 541 to receive imipenem-cilastatin. Seventy-five U.S. sites and 17 foreign sites enrolled patients; no U.S. site enrolled more than 8% of the patients, and no foreign site enrolled more than 6%. Thirty-nine patients did not receive study drug, most commonly because of failure to meet enrollment criteria. Table 2 shows the demographic characteristics of the ITT population.

Table 2. Demographic Characteristics

	Meropenem (N=510)		**Imipenem-cilastatin (N=527)**	
	n	(%)	n	(%)
Sex				
Male	303	(59)	322	(61)
Female	207	(41)	205	(39)
Age (years)				
13 to 16	3	(1)	3	(1)
17 to 44	200	(39)	217	(41)
45 to 64	215	(42)	213	(40)
65 to 74	55	(11)	47	(9)
≥75	37	(7)	47	(9)
Mean	48.8		48.5	
Range	14 to 91		13 to 95	
Race				
White	239	(47)	253	(48)
Black	135	(27)	143	(27)
Asian	19	(4)	23	(4)
Hispanic	56	(11)	50	(10)
Other	61	(12)	58	(11)
Country (number of sites)				
United States (75)	366	(72)	380	(72)
Canada (6)	16	(3)	19	(4)
South Africa (8)	125	(25)	126	(24)
Brazil (3)	3	(1)	2	(<1)

Adapted from 3591IL/0079 study report, Table 23

Comment: Demographic characteristics were evenly distributed between groups.

Table 3 summarizes selected baseline characteristics of the treated patients.

Table 3. Baseline Patient Characteristics

	Meropenem (N=510)		Imipenem-cilastatin (N=527)	
	n	(%)	n	(%)
General condition				
Good	219	(43)	225	(43)
Fair	250	(49)	255	(48)
Poor	40	(8)	44	(8)
Critical	-		3	(1)
Current medical condition				
Diabetes mellitus	195	(38)	183	(35)
Peripheral vascular disease	56	(11)	68	(13)
Recurring cellulitis	45	(9)	40	(8)
Chronic skin ulcers	38	(8)	46	(9)
Congestive heart failure	34	(7)	43	(8)
Venous stasis disease	22	(4)	33	(6)
Prior surgery related to SSSI				
Any surgery	121	(24)	122	(23)
Incision and drainage	54	(11)	40	(8)
Amputation	23	(5)	28	(5)
Debridement	17	(3)	23	(4)
Infection diagnosis				
Complex abscess	212	(42)	219	(42)
Wound infection	91	(18)	101	(19)
Cellulitis	88	(17)	89	(17)
Infected diabetic/ischemic ulcer	51	(10)	44	(8)
Perirectal abscess	37	(7)	42	(8)
Other	30	(6)	32	(6)
Initial surgical intervention				
Any surgery	346	(68)	368	(70)
Incision and drainage	275	(54)	278	(53)
Operative debridement	71	(14)	84	(16)
Other	34	(7)	52	(10)
Amputation	11	(2)	6	(1)
Wound closure	-		1	(<1)

Adapted from 3591IL/0079 study report, Table 24

Comment: Major baseline characteristics, including types of SSSI and surgical interventions, were similar between groups.

6.1.4.2 Evaluability

Table 4 summarizes the applicant's determinations of the MITT and clinically evaluable analysis sets. Most of the exclusions due to resistant pathogens were because of isolation of methicillin-resistant *Staphylococcus aureus*.

Table 4. Applicant's Accounting of Patient Evaluability

ITT population	Meropenem (N=510)		Imipenem-cilastatin (N=527)	
	n	(%)	n	(%)
MITT evaluable	334	(65.5)	358	(67.9)
MITT exclusions*	176	(34.5)	169	(32.1)
Resistant pathogen; lack of proper C/S testing	84		98	
Failure to meet definition of cSSSI	58		56	
Lack of positive culture if >24 h prior therapy	41		33	
Osteomyelitis	12		13	
Peripheral vascular disease with amputation	11		4	
Necrotizing fasciitis	5		1	
Pregnancy	4		3	
Lack of informed consent	3		2	
Prior anaphylaxis to β-lactam agent	1		1	
Concurrent antiepileptic medication	1		0	
SSSI with high cure rate with local therapy	1		1	
Another focus of infection requiring therapy	1		0	
Decubitus ulcer	0		1	
Neutropenia	0		1	

MITT population	Meropenem (N=334)		Imipenem-cilastatin (N=358)	
	n	(%)	n	(%)
Clinically evaluable	261	(78.1)	287	(80.2)
Clinically unevaluable	73	(21.9)	71	(19.8)
Follow-up not performed or outside window	35		30	
Intravenous therapy <72 h	19		25	
Concomitant systemic antimicrobial therapy	12		16	
Antibiotic pretreatment >24 h	3		0	
Missed 2 consecutive doses of therapy	2		0	
No pretreatment culture	1		0	
No signs and symptoms reported	1		0	

* Patients may have failed more than one inclusion or exclusion criterion
C/S = culture and susceptibility; cSSSI = complicated skin and skin structure infection

Adapted from 3591IL/0079 study report, Table 11.1.1.5.2 and Table 22

Comment: This medical officer performed a blinded review of a random sample of 10% of the case report forms (CRFs) from this trial to verify the accuracy of the transcription of data from the CRFs to the database and to check for agreement with the applicant's evaluability and outcome determinations. This reviewer found that the key data transcriptions and outcome assessments were accurate. Two issues regarding the applicant's evaluability determinations necessitated the review of additional CRFs.

Some patients who were identified as having osteomyelitis, necrotizing fasciitis, or severe peripheral vascular disease requiring amputation received prolonged study therapy before being withdrawn from the trial and were considered to be nonevaluable. For these patients, it was often unclear whether these conditions represented treatment failure or were pre-existing conditions that should have been excluded. The protocol did not specify a time frame for diagnosis of these conditions. This reviewer believes that 72

hours is a sufficient time to make these diagnoses and that patients treated beyond this time should be considered treatment failures. The CRFs of patients receiving prolonged therapy and of those who were determined to have osteomyelitis, necrotizing fasciitis, or severe vascular disease requiring amputation were requested and reviewed. Patients who received prolonged therapy before the exclusionary diagnosis was made were placed into the clinically evaluable set.

The initial CRF review also revealed the inclusion of a number of patients who did not appear to fulfill the protocol definition of complicated SSSI. This group included patients with cellulitis who appeared to lack the additional criteria required for the diagnosis of complicated cellulitis and patients with complicated cellulitis, wound infections, and infected ulcers who did not have evidence of fever or leukocytosis. In most cases, the applicant considered these protocol deviations to be minor and permitted inclusion of these patients. It should be noted, however, that the protocol definitions had been negotiated with the applicant early in the performance of this trial and had also been made less strict at the applicant's request (in protocol amendment 1, from a requirement for fever ***and*** *leukocytosis to fever* ***or*** *leukocytosis). This reviewer believes that evidence of a systemic inflammatory response is an important criterion that helps differentiate complicated from uncomplicated SSSI. The CRFs of patients who appeared to lack complicating factors for cellulitis and of patients with cellulitis, wound infections, or infected ulcers who lacked fever or leukocytosis were requested and reviewed. Patients who lacked sufficient evidence of a complicated SSSI as defined in the protocol were made nonevaluable.*

All CRF reviews were blinded to treatment assignment (CRFs did not identify treatment). One hundred CRFs were reviewed in addition to the random sample. The result of the medical officer review was a net decrease of 15 patients in the clinically evaluable set and of 25 patients in the MITT set. In the following section, results are presented from both the applicant's and the reviewer's analyses. The medical officer changes do not affect the primary endpoint analyses significantly.

6.1.4.3 Results

Clinical outcomes

The primary endpoint for this trial was clinical outcome at the post-treatment follow-up visit 7 to 14 days after completion of therapy; analyses of the clinically evaluable and MITT populations were considered co-primary. Table 5 shows the proportions of patients with satisfactory clinical outcomes at follow-up. For clinically evaluable patients, cure rates were 86.2% for meropenem and 82.9% for imipenem-cilastatin in the applicant's analysis and 85.4% and 81.4%, respectively, in the medical officer's analysis. For patients in the MITT set, cure rates were 73.1% for meropenem and 74.9% for imipenem-cilastatin in the applicant's analysis and 72.4% and 73.5%, respectively, in the medical officer's analysis. For all analyses, the lower limits of the 95% CIs around the treatment differences were greater than -10%.

Table 5. Clinical Outcomes at Follow-Up (Clinically Evaluable and MITT)

	Meropenem			Imipenem-cilastatin			Difference	
Analysis set	N	n	%	N	n	%	%	(95% CI)
Clinically evaluable								
Applicant	261	225	86.2	287	238	82.9	3.3	(-2.8, 9.3)
Medical Officer	254	217	85.4	279	227	81.4	4.0	(-2.2, 10.4)
MITT								
Applicant	334	244	73.1	358	268	74.9	-1.8	(-8.4, 4.7)
Medical Officer	323	234	72.4	344	253	73.5	-1.1	(-7.8, 5.6)

N = total; n = number with satisfactory outcome; CI = confidence interval

Adapted from 3591IL/0079 study report, Table 26

Comment: Although the point estimates for the treatment differences in the MITT analyses become negative, the lower limits of the 95% CIs for the differences remain greater than -10%. The changes in the medical officer's analysis sets do not significantly affect the study results or their interpretation. These analyses support the conclusion that meropenem is noninferior to imipenem-cilastatin for the treatment of complicated SSSI.

The major secondary endpoints included clinical outcomes at the post-treatment follow-up visit in the fully evaluable, microbiologic MITT, microbiologic ITT, and ITT populations. Table 6 shows the proportions of patients in these populations with satisfactory clinical outcomes at follow-up.

Table 6. Clinical Outcomes at Follow-Up (Fully Evaluable, Microbiologic MITT, Microbiologic ITT, ITT)

	Meropenem			Imipenem-cilastatin			Difference	
Analysis set	N	n	%	N	n	%	%	(95% CI)
Fully evaluable								
Applicant	209	185	88.5	231	192	83.1	5.4	(-1.1, 11.9)
Medical Officer	209	181	86.6	229	186	81.2	5.4	(-1.5, 12.2)
Microbiologic MITT								
Applicant	279	205	73.5	303	225	74.3	-0.8	(-7.9, 6.4)
Medical Officer	274	200	73.0	298	218	73.2	-0.2	(-7.4, 7.1)
Microbiologic ITT								
Applicant	404	233	57.7	416	258	62.0	-4.3	(-11.1, 2.4)
Medical Officer	403	232	57.6	415	256	61.7	-4.1	(-10.8, 2.6)
ITT								
Applicant	510	295	57.8	527	325	61.7	-3.8	(-9.8, 2.1)
Medical Officer	510	295	57.8	527	321	60.9	-3.1	(-9.0, 2.9)

N = total; n = number with satisfactory outcome; CI = confidence interval

Adapted from 3591IL/0079 study report, Table 30

Comment: These analyses are consistent with the primary endpoint analyses. There are no significant differences between the applicant's and the medical officer's findings.

Table 7 provides a breakdown of clinical outcomes by infection diagnosis. Cure rates were highest for patients with complex or perirectal abscesses and lowest for patients with infected diabetic or ischemic ulcers.

Table 7. Clinical Outcomes at Follow-Up by Infection Diagnosis (Clinically Evaluable)

	Meropenem			Imipenem-cilastatin		
Diagnosis	N	n	%	N	n	%
Cellulitis						
Applicant	39	26	66.7	42	33	78.6
Medical Officer	35	23	65.7	34	26	76.5
Complex abscess						
Applicant	125	120	96.0	126	116	92.1
Medical Officer	125	120	96.0	129	116	89.9
Perirectal abscess						
Applicant	21	18	85.7	30	28	93.3
Medical Officer	21	18	85.7	30	28	93.3
Wound infection						
Applicant	44	36	81.8	49	35	71.4
Medical Officer	43	35	81.4	45	31	68.9
Infected diabetic/ischemic ulcer						
Applicant	17	12	70.6	20	11	55.0
Medical Officer	14	8	57.1	21	11	52.4
Other						
Applicant	15	13	86.7	20	15	75.0
Medical Officer	16	13	81.3	20	15	75.0

N = total; n = number with satisfactory outcome

Adapted from 3591IL/0079 study report, Table 31

Comment: Cure rates for abscesses are most likely higher because of the contribution of surgical management and because these patients are younger and have fewer comorbidities than patients with other types of complicated SSSI. The observed differences between treatment groups are not likely to be clinically significant.

The applicant provided an analysis of clinical outcomes in patients requiring dosage adjustments because of renal impairment. Clinical response rates at follow-up were 71.4% for 21 clinically evaluable meropenem patients and 73.5% for 34 clinically evaluable imipenem-cilastatin patients. These rates were approximately 10% to 15% lower than those of patients not requiring dosage adjustments. Patients with renal dosage adjustments were more likely to have comorbidities and infection diagnoses associated with lower response rates (i.e., cellulitis and infected ulcers).

The applicant also analyzed clinical outcomes according to initial surgical intervention. In both treatment groups, response rates at follow-up were 15% to 20% greater in patients who underwent an initial surgical intervention. There were no significant differences between treatments when patients were grouped by presence or absence of an initial intervention.

Table 8 shows the applicant's analysis of clinical outcomes by age, gender, and race. There were no significant differences between treatment groups in the clinical response rates in any of these demographic categories.

Table 8. Clinical Outcomes at Follow-Up by Age, Gender, and Race (Clinically Evaluable)

	Meropenem			Imipenem-cilastatin		
Demographic group	N	n	%	N	n	%
All patients	261	225	86.2	287	238	82.9
Age						
<65 years	218	190	87.2	241	205	85.1
≥65 years	43	35	81.4	46	33	71.7
≥75 years	18	15	83.3	19	13	68.4
Gender						
Male	148	130	87.8	172	137	79.7
Female	113	95	92.0	115	101	87.8
Race						
White	104	78	75.0	132	101	76.5
Black	75	72	96.0	87	77	88.5
Asian	15	13	86.7	16	14	87.5
Hispanic	30	27	90.0	16	15	93.8
Other	37	35	94.6	36	31	86.1

N = total; n = number with satisfactory outcome

Adapted from 3591IL/0079 study report, Tables 33, 34, and 11.2.1.9.1

For clinically evaluable patients from U.S. sites, cure rates at follow-up were 80.0% (132/165) for meropenem recipients and 77.9% (134/172) for imipenem-cilastatin recipients (treatment difference, 2.1%; 95% CI, -6.6, 10.8). For clinically evaluable patients from outside the U.S., the corresponding cure rates were 96.9% (93/96) and 90.4% (104/115), respectively. The applicant attributed the higher cure rates observed in sites outside the U.S. to proportionately greater enrollment of younger patients with complex abscesses. For example, from South African sites, 67.2% (127/189) of clinically evaluable patients had complex abscesses, compared with 35.3% (119/ 337) of patients from U.S. sites.

> *Comment: Elimination of non-U.S. sites does not significantly affect the comparison between treatments; the 95% CI for the treatment difference remains greater than -10% when only U.S. sites are considered.*

Microbiologic outcomes

Microbiologic endpoints included microbiologic and pretreatment pathogen outcomes at follow-up in the microbiologically evaluable populations. Table 9 shows the proportions of patients in these populations with satisfactory microbiologic outcomes at follow-up.

Table 9. Microbiologic Outcomes at Follow-Up (Fully Evaluable, Microbiologic MITT, Microbiologic ITT)

	Meropenem			Imipenem-cilastatin			Difference	
Analysis set	N	n	%	N	n	%	%	(95% CI)
Fully evaluable								
Applicant	209	166	79.4	231	183	79.2	0.2	(-7.4, 7.8)
Medical Officer	209	163	78.0	229	178	77.7	0.3	(-7.5, 8.1)
Microbiologic MITT								
Applicant	279	182	65.2	303	207	68.3	-3.1	(-10.7, 4.6)
Medical Officer	274	178	65.0	298	201	67.4	-2.4	(-10.3, 5.3)
Microbiologic ITT								
Applicant	404	209	51.7	416	236	56.7	-5.0	(-11.8, 1.8)
Medical Officer	403	208	51.6	415	235	56.6	-5.0	(-11.8, 1.8)

N = total; n = number with satisfactory outcome; CI = confidence interval

Adapted from 3591IL/0079 study report, Table 38

Comment: These analyses are consistent with the primary endpoint analyses. There are no significant differences between the applicant's and the medical officer's findings.

Clinical and microbiologic outcomes in fully evaluable patients were concordant in 91% of meropenem recipients and 96% of imipenem-cilastatin recipients. All discordant outcomes were in patients who had satisfactory clinical outcomes and unsatisfactory microbiologic outcomes; the most common microbiologic outcome in this setting was documented persistence of a pathogen. The difference between meropenem and imipenem-cilastatin in concordance rates was due to the more frequent persistence of *Staphylococcus aureus* in meropenem patients.

Table 10 shows the proportions of patients with satisfactory pretreatment pathogen outcomes and clinical outcomes at follow-up for the pathogens included in the proposed label. The results presented are the applicant's; the corresponding analysis using the medical officer's evaluability and outcome determinations does not differ significantly and is not reproduced. The most commonly isolated pathogen was *S. aureus*.

Table 10. Pretreatment Pathogen Outcomes and Clinical Outcomes at Follow-Up for Pathogens in Proposed Label (Fully Evaluable)

	Meropenem (N=209)					Imipenem-cilastatin (N=231)				
		Pretreatment pathogen outcome		Clinical outcome			Pretreatment pathogen outcome		Clinical outcome	
Pathogen	N	n	%	n	%	N	n	%	n	%
Gram-positive aerobes										
Staphylococcus aureus, methicillin susceptible	88	69	78	82	93	100	83	83	84	84
Streptococcus pyogenes (Group A)	29	27	93	26	90	32	29	91	28	88
Streptococcus agalactiae (Group B)	17	14	82	12	71	19	16	84	16	84
Enterococcus faecalis	12	9	75	9	75	20	13	65	14	70
Viridans streptococci, nos	12	11	92	11	92	6	5	83	5	83
Streptococcus milleri	5	4	80	4	80	11	11	100	11	100
Gram-negative aerobes										
Escherichia coli	15	12	80	12	80	21	14	67	15	71
Pseudomonas aeruginosa	15	10	67	11	73	15	14	93	13	87
Proteus mirabilis	13	11	85	11	85	7	5	71	6	86
Anaerobes										
Bacteroides fragilis	11	10	91	10	91	10	9	90	9	90
Peptostreptococcus spp.	13	10	77	10	77	16	14	88	14	88

N = number of patients; n = number with satisfactory outcome; nos = not otherwise specified

Adapted from 3591IL/0079 study report, Table 41

*Comment: Pretreatment pathogen outcomes and clinical outcomes were generally similar between treatment groups with the notable exception of patients with Pseudomonas aeruginosa. For patients with P. aeruginosa, the eradication rate was only 67% (10/15) with meropenem, compared with 93% (14/15) with imipenem-cilastatin; clinical response rates were 73% (11/15) with meropenem and 87% (13/15) with imipenem-cilastatin. The pathogen eradication rate and clinical response rate for patients with P. aeruginosa treated with meropenem are also lower than the microbiologic and clinical response rates of fully evaluable meropenem patients overall. This information should be included in the **CLINICAL STUDIES** section of the labeling.*

6.1.5 Clinical Microbiology

[redacted]

6.1.6 Efficacy Conclusions

In Study 3591IL/0079, the applicant has demonstrated that meropenem 500 mg iv q8h is noninferior to imipenem-cilastatin 500 mg iv q8h for the treatment of complicated SSSI. The results of this study, together with the findings of the skin blister pharmacokinetic study, support the approval of meropenem for the treatment of complicated SSSI due to *Staphylococcus aureus* (methicillin susceptible strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, viridans streptococci, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety analysis set in Study 3591IL/0079 includes all patients who received at least one dose of study drug. This analysis set differs from the ITT set by three patients: one patient randomized to receive meropenem was treated with imipenem-cilastatin throughout the study, and two patients randomized to receive imipenem-cilastatin were treated with meropenem throughout the study. In this trial, 511 patients received at least one dose of meropenem (mean 5.8 days, range 1 to 17 days), and 526 patients received at least one dose of imipenem-cilastatin (mean 6.0 days, range 1 to 20 days).

Adverse events (AEs) were recorded daily during study drug administration and at the post-treatment follow-up visit. Laboratory testing of hematologic status and renal and hepatic function was performed at study entry, during study therapy as needed, at the end of study therapy, and at follow-up as needed.

The dose of meropenem in this study, 500 mg q8h, is one-half the dose in the approved labeling for intraabdominal infections. The most frequently reported AEs in patients receiving meropenem were headache, nausea, constipation, and diarrhea. The most frequently reported drug-related AE in patients receiving meropenem was diarrhea. The overall safety profile for meropenem in this study is similar to that of imipenem-cilastatin. The applicant updated the **ADVERSE REACTIONS** section of the proposed labeling by including a paragraph summarizing the most commonly reported AEs in this study. No other changes in safety labeling for meropenem are recommended based on review of the findings of this study.

7.1.1 Deaths

The applicant reported 19 deaths in the 1037 patients who received study drug, including 10 of 511 (2.0%) meropenem recipients and 9 of 526 (1.7%) imipenem-cilastatin recipients. Seven deaths (4 in the meropenem group and 3 in the imipenem-cilastatin group) were in patients greater than 75 years of age. Most deaths occurred more than 7 days after the last dose of study therapy, with a median of 11 days (range 1 to 46 days) in the meropenem group and 14 days (range 1 to 28 days) in the imipenem-cilastatin group. Deaths in meropenem recipients were attributed to congestive heart failure (3 patients), cardiac arrest or arrhythmia (2 patients), sepsis (2 patients), acute respiratory failure, cerebrovascular accident, and pulmonary embolism (1 patient each). None of the deaths in either treatment group were considered by the investigators to be drug-related.

Comment: This medical officer reviewed the CRFs and summaries of these patients and concurs with the investigators' assessments.

7.1.2 Other Serious Adverse Events

Table 11 shows the nonfatal serious AEs (SAEs) that were reported in at least two patients in either group. The applicant reported nonfatal SAEs in 35 patients in the meropenem group and in 39 patients in the imipenem-cilastatin group. The SAE profiles are generally comparable between groups.

Table 11. Nonfatal Serious Adverse Events Occurring in at Least Two Patients in Either Treatment Group

	Meropenem (N=511)		**Imipenem-cilastatin (N=526)**	
Body system/COSTART preferred term	n	%	n	%
Patients with any nonfatal SAE	35	6.8	39	7.4
Whole body system				
Abscess	2	0.4	2	0.4
Allergic reaction	2	0.4	0	-
Cellulitis	2	0.4	2	0.4
Sepsis	1	0.2	4	0.8
Cardiovascular system				
Peripheral vascular disorder	5	1.0	2	0.4
Hypotension	2	0.4	1	0.2
Atrial fibrillation	2	0.4	0	-
Cerebral ischemia	0	-	2	0.4
Musculoskeletal system				
Osteomyelitis	3	0.6	2	0.4
Respiratory system				
Pneumonia	1	0.2	4	0.8
Urogenital system				
Kidney failure	2	0.4	2	0.4
Metabolic and nutritional system				
Hypoglycemia	3	0.6	0	-

Adapted from 3591IL/0079 study report, Table 60

Three patients in the meropenem group and 2 patients in the imipenem-cilastatin group had SAEs that were considered by the investigators to be drug-related. One meropenem recipient developed atrial fibrillation and 2 patients had allergic reactions during the iv treatment phase. One imipenem-cilastatin patient developed acute renal failure during the iv treatment phase, and another patient developed *Clostridium difficile* colitis with onset 18 days following the last dose of iv treatment.

7.1.3 Dropouts and Other Significant Adverse Events

Table 12 shows the AEs that led to withdrawal from the study; the incidence is similar between treatment groups.

Table 12. Adverse Events Leading to Withdrawal

	Meropenem (N=511)		**Imipenem-cilastatin (N=526)**	
Body system/COSTART preferred term	n	%	n	%
Patients with AEs leading to withdrawal	13	2.5	14	2.7
Cardiovascular system				
Peripheral vascular disorder	2	0.4	1	0.2
Cerebrovascular accident	1	0.2	0	-
Pulmonary embolus	1	0.2	0	-
Sinus bradycardia	1	0.2	0	-
Whole body system				
Allergic reaction	2	0.4	0	-
Sepsis	1	0.2	1	0.2
Accidental injury	0	-	2	0.4
Hostility	0	-	1	0.2
Skin and appendages				
Rash	2	0.4	0	-
Urticaria	2	0.4	1	0.2
Digestive system				
Nausea	1	0.2	4	0.8
Vomiting	1	0.2	1	0.2
Diarrhea	0	-	1	0.2
Musculoskeletal system				
Osteomyelitis	1	0.2	0	-
Metabolic and nutritional system				
Creatinine increased	0	-	1	0.2
Nervous system				
Anxiety	0	-	1	0.2
Respiratory system				
Pneumonia	0	-	1	0.2

Adapted from 3591IL/0079 study report, Table 62

Two meropenem patients had two AEs leading to withdrawal (rash and urticaria, nausea and vomiting); one imipenem-cilastatin patient had two AEs leading to withdrawal (nausea and vomiting). All but three of the AEs leading to withdrawal occurred during the iv treatment phase. Five patients in the meropenem group were withdrawn following AEs that were considered by the investigators to be drug-related: these patients had allergic reactions (2 patients), rash and urticaria, rash alone, and urticaria alone (1 patient each). Six patients in the

imipenem-cilastatin group were withdrawn following AEs that were considered by the investigators to be drug-related: these patients had nausea alone (2 patients), nausea and vomiting, vomiting alone, urticaria, and elevated creatinine (1 patient each).

7.1.5 Common Adverse Events

Table 13 lists the AEs that were reported in at least 1% of the patients in either treatment group. At least one AE was reported in 297 patients (58.1%) in the meropenem group and in 298 patients (56.7%) in the imipenem-cilastatin group.

Table 13. Adverse Events Occurring in at Least 1% of Either Treatment Group

COSTART preferred term	Meropenem (N=511) n	%	Imipenem-cilastatin (N=526) n	%
Headache	40	7.8	33	6.3
Nausea	40	7.8	57	10.8
Constipation	36	7.0	44	8.4
Diarrhea	36	7.0	32	6.1
Anemia	28	5.5	21	4.0
Pain	26	5.1	20	3.8
Pruritis	25	4.9	31	5.9
Vomiting	25	4.9	26	4.9
Injection site reaction	21	4.1	21	4.0
Fever	18	3.5	18	3.4
Insomnia	17	3.3	22	4.2
Rash	16	3.1	20	3.8
Vaginal moniliasis*	6	2.9	6	2.9
Hypertension	13	2.5	13	2.5
Chest pain	12	2.3	6	1.1
Dyspnea	12	2.3	9	1.7
Dizziness	10	2.0	10	1.9
Hypotension	10	2.0	11	2.1
Peripheral edema	10	2.0	7	1.3
Anorexia	9	1.8	1	0.2
Hypokalemia	9	1.8	17	3.2
Pharyngitis	9	1.8	5	1.0
Accidental injury	8	1.6	7	1.3
Agitation	8	1.6	2	0.4
Anxiety	8	1.6	8	1.5
Asthenia	8	1.6	2	0.4
SGOT (AST) increased	8	1.6	15	2.9
SGPT (ALT) increased	8	1.6	13	2.5
Abdominal pain	7	1.4	7	1.3
Asthma	7	1.4	6	1.1
Confusion	7	1.4	5	1.0
Cough increased	7	1.4	8	1.5
Gastrointestinal disorder	7	1.4	4	0.8
Hypoglycemia	7	1.4	5	1.0
Peripheral vascular disorder	7	1.4	2	0.4
Depression	6	1.2	5	1.0
Dyspepsia	6	1.2	4	0.8
Leukocytosis	6	1.2	2	0.4
Pneumonia	6	1.2	4	0.8
Thrombocytopenia	6	1.2	5	1.0
Sepsis	5	1.0	7	1.3
Back pain	4	0.8	10	1.9
Lung disorder	4	0.8	7	1.3

* Number of female patients: meropenem, 207; imipenem-cilastatin, 205

Adapted from 3591IL/0079 study report, Table 50

The most commonly reported AEs in meropenem patients were headache, nausea, constipation, diarrhea, anemia, and pain. The most commonly reported AEs in imipenem-cilastatin patients were nausea, constipation, headache, diarrhea, and pruritis. The incidence of specific AEs was

generally similar between groups. Most AEs occurred during the iv treatment phase, and most were described as mild to moderate in intensity.

Table 14 lists the AEs that were considered by investigators to be drug-related and that occurred in at least 2 patients in either treatment group. Drug-related AEs were reported in 9.0% of meropenem patients and 10.8% of imipenem-cilastatin patients. Diarrhea was the most commonly reported drug-related AE in both treatment groups.

Table 14. Drug-Related Adverse Events Occurring in at Least Two Patients in Either Treatment Group

	Meropenem (N=511)		**Imipenem-cilastatin (N=526)**	
Body system/COSTART preferred term	n	%	n	%
Patients with any drug-related AE	46	9.0	57	10.8
Digestive system				
Diarrhea	11	2.2	13	2.5
Nausea	4	0.8	11	2.1
Oral moniliasis	3	0.6	2	0.4
Constipation	1	0.2	2	0.4
Vomiting	1	0.2	6	1.1
Whole body system				
Headache	3	0.6	3	0.6
Allergic reaction	2	0.4	0	-
Fever	2	0.4	0	-
Skin and appendages				
Rash	3	0.6	3	0.6
Urticaria	3	0.6	1	0.2
Pruritis	2	0.4	8	1.5
Fungal dermatitis	0	-	2	0.4
Hemic and lymphatic system				
Thrombocytopenia	4	0.8	2	0.4
Urogenital system				
Vaginal moniliasis	4	0.8	5	1.0
Vaginitis	0	-	2	0.4
Metabolic and nutritional system				
SGPT increased	3	0.6	8	1.5
SGOT increased	2	0.4	10	1.9

Adapted from 3591IL/0079 study report, Table 11.3.2.3.1

The applicant analyzed AEs by age, gender, and race.

AEs were reported more frequently in patients ≥65 years of age than in patients <65 years of age. In the meropenem group, AEs were reported in 64.5% of patients ≥65 years of age and 56.7% of patients <65 years of age; in the imipenem-cilastatin group, AEs were reported in 71.0% and 53.6%, respectively. In the meropenem group, constipation was the only AE for which there was a ≥5% increase in incidence in patients ≥65 years of age (12.9% vs. 5.7%). In the imipenem-cilastatin group, the following AEs had a ≥5% increase in incidence in patients ≥65 years of age: constipation (19.4% vs. 6.0%), diarrhea (10.8% vs. 5.1%), dyspnea (6.5% vs. 0.7%), and back pain (6.5% vs. 0.9%). Meropenem patients ≥65 years of age were less frequently reported to

have constipation and nausea than were imipenem-cilastatin patients ≥65 years of age. The AE profile of patients ≥75 years of age was similar to that of patients ≥65 years of age for each drug.

AEs were reported more frequently in female patients than in male patients. In the meropenem group, AEs were reported in 64.3% of female patients and 53.9% of male patients; in the imipenem-cilastatin group, AEs were reported in 67.3% and 49.8%, respectively. In the meropenem group, the following AEs had a ≥5% increase in incidence in female patients: constipation (11.1% vs. 4.3%), nausea (11.1% vs. 5.6%), and vomiting (8.7% vs. 2.3%). In the imipenem-cilastatin group, the following AEs had a ≥5% increase in incidence in female patients: nausea (18.0% vs. 6.2%) and constipation (11.7% vs. 6.2%). Female meropenem patients were less frequently reported to have nausea than were female imipenem-cilastatin patients.

AEs were reported most frequently in white patients. In the meropenem group, AEs were reported in 63.6% of white patients, 47.0% of black patients, and 59.4% of other patients (Hispanic, Asian, and all others); in the imipenem-cilastatin group, AEs were reported in 62.8%, 53.5%, and 48.1%, respectively. The only AEs for which one racial group had a ≥5% difference in incidence compared with the other groups were pain in meropenem patients (12.3% other, 3.3% white, and 0.7% black) and diarrhea in imipenem-cilastatin patients (9.9% white, 3.5% black, and 1.6% other).

7.1.7 Laboratory Findings

Table 15 shows the proportions of patients with clinically significant changes from baseline hematology values. Clinically significant changes were defined as follows: hemoglobin decrease ≥2.5 g/dL; hematocrit decrease ≥8%; total WBC count decrease to <4000/mm^3 if pretreatment WBC count was ≥4000/mm^3 or decrease of ≥1000/mm^3 if baseline WBC count was <4000/mm^3; eosinophil increase to ≥5%; platelet count decrease of ≥25,000/mm^3 if baseline was <100,000/mm^3 or value of <100,000/mm^3 if baseline was ≥100,000/mm^3; and platelet count increase to >500,000/mm^3 if baseline was <500,000/mm^3. The proportions of patients with clinically significant changes from baseline were similar between groups.

Table 15. Proportion of Patients with Clinically Significant Changes from Baseline in Hematology Values

Laboratory value	Meropenem (N=511) N	n	%	Imipenem-cilastatin (N=526) N	n	%
During therapy to end of treatment visit						
Eosinophils	403	35	8.7	414	32	7.7
Hemoglobin	460	32	7.0	471	33	7.0
Hematocrit	460	32	7.0	473	27	5.7
Platelet count decrease	448	5	1.1	455	4	0.9
Platelet count increase	448	42	9.4	455	48	10.5
Total WBC count decrease	453	21	4.6	465	15	3.2
After end of treatment visit						
Eosinophils	146	12	8.2	147	10	6.8
Hemoglobin	160	7	4.4	165	7	4.2
Hematocrit	159	5	3.1	165	5	3.0
Platelet count decrease	151	3	2.0	155	1	0.6
Platelet count increase	151	7	4.6	155	1	0.6
Total WBC count decrease	155	8	5.2	157	3	1.9

Adapted from 3591IL/0079 study report, Table 64

Table 16 shows the proportions of patients with clinically significant changes from baseline chemistry values. Clinically significant changes were defined as follows: creatinine increase of ≥0.2 mg/dL; AST increase of ≥3 times baseline; and ALT increase of ≥3 times baseline. Among patients in whom follow-up values were obtained, a greater percentage of imipenem-cilastatin recipients had clinically significant increases in creatinine (15.0% for imipenem-cilastatin vs. 6.8% for meropenem).

Table 16. Proportion of Patients with Clinically Significant Changes from Baseline in Chemistry Values

Laboratory value	Meropenem (N=511) N	n	%	Imipenem-cilastatin (N=526) N	n	%
During therapy to end of treatment visit						
Creatinine	444	26	5.9	459	42	9.2
AST	347	10	2.9	377	21	5.6
ALT	341	18	5.3	376	20	5.3
After end of treatment visit						
Creatinine	146	10	6.8	153	23	15.0
AST	127	0	-	143	4	2.8
ALT	125	3	2.4	142	6	4.2

Adapted from 3591IL/0079 study report, Table 65

8 ADDITIONAL CLINICAL ISSUES

8.4 Pediatrics

In this efficacy supplement, the applicant is requesting a full waiver for conducting pediatric studies of meropenem for the treatment of complicated SSSI. The applicant states that pediatric studies "are impossible or highly impractical to conduct because the incidence of complicated skin and skin structure infections in this population is so small or geographically dispersed." This rationale is listed in the Pediatric Research Equity Act of 2003 as one of the possible justifications for waiver of the requirement to submit pediatric assessments for a drug. In support of this request, the applicant provided estimates of projected incidence rates for 2005 for hospitalized SSSIs in the U.S., using data from the U.S. Census Bureau and the National Institutes of Health National Hospital Discharge Survey as presented by the Mattson Jack Database. The projected incidence rates (per 1000 population) by age group are as follows: 0-9 years, 2.6/1000; 10-19 years, 2.7/1000; 20-39 years, 4.1/1000; 40-59 years, 5.9/1000; and 60+ years, 18.0/1000.

The applicant previously submitted a pediatric plan for this indication (NDA 50-706; 8/12/03). In this assessment, the applicant proposed that the results from the pharmacokinetic and clinical trials included in the present efficacy supplement, along with previously submitted data from studies of meropenem in pediatric patients, would support a labeling change for the use of meropenem at a dose of 10 mg/kg q8h for complicated SSSI in pediatric patients $\geq$3 months of age. The applicant compared clinical patterns of SSSI observed in trials of meropenem in children and adults and summarized previously submitted data on the pharmacokinetics, efficacy, safety, and tolerability of meropenem in children.

As part of the original NDA for meropenem (original submission 10/28/93; resubmission 11/22/95), the applicant submitted two pediatric trials (3591US/0013 and 3591IL/0045) in which 417 patients were treated with meropenem for a variety of serious bacterial infections, excluding bacterial meningitis. These studies enrolled 59 patients with SSSI. The majority of SSSI diagnoses were cellulitis and abscesses, and the majority of pathogens isolated were *S. aureus* and *S. pyogenes*. In the applicant's previous studies of SSSI in adults, abscesses and cellulitis were the most common diagnoses; in the present supplement, wound infections were also common. In the adult studies, the most commonly isolated pathogens were also *S. aureus* and *S. pyogenes*. In other respects, SSSIs in children differ somewhat from those in adults. Children are less likely than adults to have medical conditions that predispose to complicated cellulitis; of the other types of complicated SSSI studied, infected diabetic or ischemic ulcers occur almost exclusively in adults. Children are also less likely than adults to have complicated SSSI due to Gram-negative or anaerobic bacteria.

Trial 3591US/0001 (submitted 10/28/93) evaluated the safety, tolerance, and pharmacokinetics of a single iv dose of meropenem in infants and children. In this study, 63 hospitalized children 3 months to 12 years of age received single doses of 10 mg/kg, 20 mg/kg, or 40 mg/kg. Twenty patients received the 10 mg/kg dose; the age subgroups were 3 to 5 months (n=3), 6 to 23 months

(n=5), 2 to 5 years (n=5), and 6 to 12 years (n=7). The pharmacokinetic profile of the 10 mg/kg dose in children was similar to that of a 500 mg dose in adults. All doses were well tolerated.

The two pediatric treatment trials cited above enrolled patients with intraabdominal infections (IAI), lower respiratory tract infections (LRTI), urinary tract infections (UTI), bacterial septicemia, and SSSI. These trials were not designed to assess efficacy in each infection adequately; the plan was to use these safety and efficacy results along with pharmacokinetic data to extrapolate adult efficacy data to the pediatric population. Because of issues related to trial conduct, most patients in the adult studies were nonevaluable, and only the IAI indication was approved. Consequently, in the pediatric trials, only the patients with IAI were reviewed in detail for efficacy. All patients were included in safety analyses, however. In Trial 3591US/0013, the meropenem dose was 20 mg/kg q8h. The applicant reported a satisfactory clinical response rate at follow-up of 91% (38/42) for SSSI patients treated with meropenem, compared with 100% (32/32) for SSSI patients treated with cefotaxime. There were no evaluable patients in Trial 3591IL/0045 with SSSI; the dose of meropenem in this trial was 10 mg/kg q8h for UTI, SSSI, and community-acquired LRTI and 20 mg/kg for IAI, bacterial septicemia, hospital-acquired LRTI, and other infections.

In these trials, 417 pediatric patients were treated with 10 mg/kg or 20 mg/kg doses of meropenem for serious bacterial infections. The safety profile of meropenem was similar to that of the comparator, cefotaxime. The most common treatment-related AEs were diarrhea, rash, nausea, and vomiting. In the bacterial meningitis trials, 321 pediatric patients were treated with a meropenem dose of 40mg/kg q8h. The safety profile of meropenem was similar to that of the comparators (cefotaxime or ceftriaxone). The most common treatment-related AEs were diarrhea, rash, oral moniliasis, and glossitis. In the meningitis trials, seizure rates during therapy were comparable between patients with no central nervous system abnormalities who received meropenem and those who received comparators. The current pediatric labeling for meropenem contains the AE information from both sets of studies.

> *Comment: For the treatment of complicated SSSI with meropenem, the course of the disease and the effects of the drug are sufficiently similar to permit extrapolation of adult efficacy data to the pediatric population. The pharmacokinetic and safety data from the previous trials support a dose of meropenem of 10 mg/kg q8h for pediatric patients ≥3 months of age. The* ***Pediatric Use*** *section of the current label should be modified to state, "Use of MERREM I.V. in pediatric patients with intra-abdominal and skin and skin structure 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." The* ***ADVERSE REACTIONS*** *section of the current label already summarizes the safety information from the pediatric serious bacterial infection trials that used doses of 10-20 mg/kg q8h, as well as from the meningitis trials that used a 40 mg/kg q8h dose. No additional information is available, and no changes in pediatric safety labeling are necessary. The pediatric SSSI dose must also be added to the* ***DOSAGE AND ADMINISTRATION*** *section.*

This reviewer recommends granting the applicant a partial waiver of the requirement to submit an assessment for pediatric patients <3 months of age on the grounds that the necessary studies are impracticable because the incidence of complicated SSSI in this population is so small and the patients are geographically dispersed. Furthermore, meropenem does not represent a meaningful therapeutic benefit over existing therapies in this age group, and it is not likely to be used in a substantial number of patients for this indication in this age group.

9 OVERALL ASSESSMENT

9.1 Conclusions

Meropenem, 500 mg iv q8h in adults and 10 mg/kg iv q8h in pediatric patients ≥3 months of age, is safe and effective therapy for the treatment of complicated SSSI due to *Staphylococcus aureus* (methicillin susceptible strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, viridans streptococci, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species.

9.2 Recommendation on Regulatory Action

This efficacy supplement may be approved.

9.3 Recommendation on Postmarketing Actions

Meropenem was approved in the U.S. in 1996 for other indications, and no changes in current postmarketing reporting requirements are recommended.

9.4 Labeling Review

The applicant's proposed labeling is generally acceptable. The following modifications are recommended:

1. The **INDICATIONS AND USAGE** section for the SSSI indication should state only those bacteria for which adequate evidence of efficacy has been provided: *Staphylococcus aureus* (methicillin susceptible strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, viridans streptococci, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species..

2. The **Pediatric Use** section should include the SSSI indication, and the **DOSAGE AND ADMINISTRATION** section should include the dose of 10 mg/kg q8h for treatment of complicated SSSI in pediatric patients ≥3 months of age.

3. The **CLINICAL STUDIES** section should delete reference to specific types of complicated SSSI and include a table of efficacy rates by pathogen. A similar table is presented for the bacterial meningitis indication.

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/s/

Thomas Smith
5/11/05 11:50:10 AM
MEDICAL OFFICER
Review of cSSSI efficacy supplement

Jean Mulinde
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Janice Soreth
5/11/05 12:31:43 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-706 / S-018

CHEMISTRY REVIEW(S)

DIVISION OF ANTI-INFECTIVES DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50706 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 27-Jan-05

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SE1-018	28-Jul-04	28-Jul-04	28-Jul-04
SE1-018/BC	04-Feb-05	7-Feb-05	____

NAME & ADDRESS OF APPLICANT:
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DRUG PRODUCT NAME

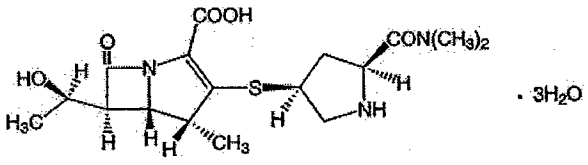
Proprietary:	MERREM® I.C. (meropenem for injection)
Nonproprietary/USAN:	Meropenem
Code Names/#'s:	ICI 194,660 - SM 7338
Chemical Type:	carbapenem antibiotic
Therapeutic Classes:	

PHARMACOLOGICAL CATEGORY/INDICATION: antimicrobial

DOSAGE FORM: parenteral
STRENGTHS: 500 mg and 1 g
ROUTE OF ADMINISTRATION: intravenous
DISPENSED: __X__ Rx ____ OTC
SPECIAL PRODUCTS: ____ Yes __X__ No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry.)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
(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.

Mol. Formula $C_{17}H_{25}N_3O_5S \bullet 3H_2O$ M.W. 437.52



REMARKS/COMMENTS:

NDA 50,706/SE1-18 is a supplemental New Drug Application for the use of 500 mg of meropenem (IV) every 7 hours as a treatment for patients with complicated skin and skin structure infections. The entire CMC is referenced to the approved NDA 50,706.

CONCLUSIONS & RECOMMENDATIONS:

NDA 50,706/SE1-18 is recommended for approval.

Rapti D. Madurawe, Ph.D.
Review Chemist

cc: Orig. NDA# 50706
HFD-520/Division File
HFD-520/ProjMan/
HFD-520/Chem/Madurawe
HFD-520/TeamLdr/Vidra

filename:

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Chemistry Review 1a

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/s/

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5/16/05 02:17:19 PM
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Jim Vidra
5/18/05 09:52:04 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-706 / S-018

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA # :	50-706
Drug Name:	MERREM® (meropenem for injection)
Indication(s):	Complicated Skin and Skin Structure Infections
Applicant:	AstraZeneca
Stamp Date:	July 28, 2004.
PDUFA Goal Date:	May 28, 2005
Reviewer Completion Date:	May 27, 2005
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III (HFD-725)
Documents Reviewed:	\\CDSESUB1\N50706\S_018\2004-07-28
Statistical Reviewer:	Christopher Khedouri, Ph.D.
Concurring Reviewer:	Thamban Valappil, Ph.D.
Medical Division:	Division of Anti-Infective Drug Products (HFD-520)
Medical Reviewer:	Thomas Smith, M.D.
Project Manager:	Susmita Samanta, M.D.

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The evidence demonstrates the non-inferiority of meropenem to imipenem-cilastatin in the treatment of patients with clinical evidence of complicated skin and skin structure bacterial infections (cSSSIs) caused by susceptible pathogens. No clinically relevant differences in cure rates were observed between meropenem and imipenem-cilastatin with respect to various covariates that included primary infection diagnosis, common pretreatment pathogens, age, gender and race. The overall safety profile for meropenem in this trial is similar to that of imipenem-cilastatin and is consistent with the current meropenem labeling.

Meropenem, 500 mg iv q8h in adults, is safe and effective therapy for patients treated for cSSSIs due to *Staphylococcus aureus* (methicillin susceptible strains), *Streptococcus pyogenes*, *Streptococcus agalactiae, viridans* group *streptococci*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species.

1.2 Brief Overview of Clinical Studies

This submission focuses on the potential efficacy of meropenem as single agent therapy for the treatment of hospitalized patients with complicated skin and skin structure infections (cSSSIs). In accordance with the *1998 FDA Draft Guidance for Uncomplicated and Complicated Skin and Skin Structure Infections – Developing Antimicrobial Drugs for Treatment*, this NDA submission includes one pivotal statistically adequate and well-controlled multi-center trial to establish safety and effectiveness (Study 3591IL/0079) and a supporting pharmacokinetic study (Study 3591IL/0091). Study 3591IL/0079 demonstrates that the drug diffuses into skin and deep soft tissue in quantities adequate to achieve tissue concentrations equal to or above the minimum inhibitory concentration for 90% of strains (MIC90) of the claimed pathogens for an adequate time period. This NDA submission also cross-references a previously conducted study 3591US/0010 (summarized in Volume 2.203 of NDA 50-706) that assessed the efficacy of meropenem for the treatment of patients with cSSSI. No other ongoing cSSSI clinical studies relevant to the indication are being conducted and no further studies are planned for the proposed indication. Study 3591IL/0079, the primary focus of this review, is a multi-center, randomized, double blind, comparative study where the primary objective is to demonstrate the therapeutic non-inferiority of meropenem (500 mg intravenous [iv] every 8 hours) to imipenem-cilastatin

(500 mg iv every 8 hours) in hospitalized patients with cSSSIs. The primary outcome is clinical outcome at the post-treatment follow-up visit.

The study demonstrated the non-inferiority of meropenem (500 mg iv every 8 hours) to imipenem-cilastatin (500mg iv every 8 hours) for treatment of hospitalized patients with complicated skin and skin structure infections. From the Medical Officer's analysis of the clinically evaluable (CE) population, the proportions of satisfactory outcomes were 85.4% (meropenem) versus 81.4% (imipenem), a 4.0% difference in proportions with a 95% CI of (-2.2, 10.4). Since the lower bound of this 95% CI is larger than the non-inferiority margin of -10%, this result demonstrated non-inferiority of meropenem to imipenem-cilastatin in the treatment of patients with clinical evidence of complicated skin and skin structure bacterial infections. Secondary analyses from the Medical Officer also demonstrate non-inferiority the MITT population, the proportions of satisfactory outcomes were 72.4% (meropenem) versus 73.5% (imipenem), a -1.1% difference with a 95% CI of (-7.8, 5.6). Note that efficacy results from the CE and MITT populations are considered co-primary in demonstrating non-inferiority.

Table 3 includes results of analyses conducted in the CE and MITT populations and secondary populations according to the sponsor and according to the FDA. An FDA analysis is included in which the Medical Officer, Dr. Thomas Smith, re-classified some of the patients with respect to the stated inclusion/exclusion criteria. However, as table 3 shows, the medical officer's analysis did not change the overall conclusion of non-inferiority of meropenem (500 mg iv every 8 hours) to imipenem-cilastatin (500mg iv every 8 hours) in the treatment of hospitalized patients with complicated skin and skin structure infections.

1.3 Statistical Issues and Findings

There were no major statistical issues. One minor issue, as previously discussed, is that the medical officer re-classified some of the patients into different analysis groups (table 3). However, these re-classifications did not change the overall results and conclusions significantly.

2. INTRODUCTION

2.1 Overview

MERREM I.V. is an anti-infective carbapenem which the sponsor claims has a wide spectrum of antibacterial activity against all clinically important gram-positive and gram-negative aerobes and anaerobes. MERREM I.V. is currently FDA approved as single agent therapy for the

treatment of complicated appendicitis and peritonitis in adults and children as well as meningitis in infants and children (≥ 3 months of age) when caused by susceptible pathogens. Outside of the U.S, MERREM I.V. at 500 mg intravenous (iv) q8h has been approved for the treatment of a variety of infections, including skin and skin structure infections (SSSIs) in over 50 countries, including the United Kingdom, Italy, and Germany. MERREM I.V. is also registered in Canada for the treatment of uncomplicated SSSIs.

[redacted] or

Study 3591IL/0079, the primary focus of this review, is a multi-center, randomized, double blind, comparative study where the primary objective is to demonstrate the therapeutic non-inferiority of meropenem (500 mg intravenous [iv] every 8 hours) to imipenem-cilastatin (500 mg iv every 8 hours) in hospitalized patients with cSSSIs. The primary outcome is clinical outcome at the post-treatment follow-up visit.

2.2 Data Sources

- The Statistical Review of NDA- 50-706
- Files of \\CDSESUB1\N50706\S_018\2004-07-28
- Minutes from all agency/sponsor discussions between Sept. 13, 2000 and Feb. 19, 2004.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Objectives

The primary objective of this study is to demonstrate the therapeutic non-inferiority of meropenem (500 mg iv every 8 hours) to imipenem-cilastatin (500 mg iv every 8 hours) in hospitalized patients with complicated skin and skin structure infections. Secondary objectives include assessing the safety and tolerability of meropenem (500 mg iv every 8 hours) administered in hospitalized patients with complicated skin and skin structure infections.

3.1.2 Study Design and Endpoints

This was a multicenter, randomized, double blind, comparative study of iv meropenem and iv imipenem-cilastatin. The target patient population was approximately 1000 hospitalized male and female patients, aged 13 years or older, with clinical evidence of complicated skin and skin structure bacterial infection with material suitable for culture, were required to be randomized to study drug in order to acquire 201 clinically evaluable patients in each treatment group. The duration of iv study treatment was expected to be from 3 to 14 days.

The Primary efficacy variable was:
- clinical outcome at the post-treatment follow-up visit.

Secondary efficacy variables were:
- clinical outcome at the post-treatment follow-up visit (excluding clinical outcomes assessed as co-primary variables)
- clinical outcome at the end-of-treatment visit
- microbiological outcome at the end-of-treatment and post-treatment follow-up visits
- pretreatment pathogen outcome at the end-of-treatment and the post-treatment follow-up visits

Safety variables were:
- incidence and severity of adverse events throughout the study
- incidence and severity of serious adverse events throughout the study
- incidence of discontinuations from the study attributed to adverse events
- laboratory parameters at the discretion of the investigator and at end-of-treatment and post-treatment follow-up visits

3.1.3 Patient Disposition, Demographic and Baseline Characteristics

Patient dispositions are summarized in table 1. Of 1076 patients who were randomized to iv study drug, 1037 received iv study drug, and 643 completed the study. Of 39 randomized

patients who did not receive iv study drug, 24 did not meet enrollment criteria: 6 patients were noncompliant with the protocol, 3 each withdrew consent and were withdrawn at the investigator's discretion, 2 were lost to follow-up, and 1 patient had a concurrent illness.

The demographic and baseline characteristics of patients in each treatment group were similar. More males were in the ITT analysis population than females, approximately 60% versus 40%. The mean age in each treatment group was 49 years; the age range in the meropenem treatment group was 14 to 91 years versus 13 to 95 years in the imipenem-cilastatin treatment group. Approximately 50% of patients in each treatment group were White, with similar distributions of other races within each treatment group. The patient population was at risk for severe consequences of complicated skin and skin structure infections. Of patients included in the ITT analysis population, 18% in each treatment group were 65 years or older, approximately 37% of patients had diabetes mellitus, and approximately 12% had peripheral vascular disease; 93% of patients in each treatment group had infections of moderate or severe intensities. Approximately 23% of all patients in the ITT analysis population had at least 1 prior surgery related to skin and skin structure infection. More than 67% of patients in each treatment group required initial surgical intervention on the primary wound site at the time of study entry. Approximately 66% of all patients in the ITT analysis population had received prior antibiotics. Among the pretreatment pathogens isolated from patients in the microbiological ITT analysis population, there were no relevant differences in *in vitro* susceptibility between meropenem and imipenem.

Table 1 Patient disposition (completion or discontinuation)

Randomized (N=1076)	
Meropenem (n=535)	Imipenem-cilastatin (n=541)
Not treated (n=25)	Not treated (n=14)
Received meropenem (n=511)	Received Imipenem-cilastatin (n=526)
Discontinued study treatment (n=204) Treatment failure (n=40) Lost to follow up (n=33) Adverse event (n=13) Concurrent illness (n=6) Protocol deviation (n=14) Failed enrollment criteria (n=79) 2nd surgical intervention <48h (n=1) Non - approved antibiotic <48h (n=4) Withdrew consent (n=9) Investigator's discretion (n=5)	Discontinued study treatment (n=109) Treatment failure (n=40) Lost to follow up (n=28) Adverse event (n=14) Concurrent illness (n=4) Protocol deviation (n=21) Failed enrollment criteria (n=60) 2nd surgical intervention <48h (n=0) Non - approved antibiotic <48h (n=6) Withdrew consent (n=11) Investigator's discretion (n=6)
Completed study (n=306)	Completed study (n=337)

Table 2 Demographic Characteristics

	Meropenem (N=510)		Imipenem-cilastatin (N=527)	
	n	(%)	n	(%)
Sex				
Male	303	(59)	322	(61)
Female	207	(41)	205	(39)
Age (years)				
13 to 16	3	(1)	3	(1)
17 to 44	200	(39)	217	(41)
45 to 64	215	(42)	213	(40)
65 to 74	55	(11)	47	(9)
≥75	37	(7)	47	(9)
Mean	48.8		48.5	
Range	14 to 91		13 to 95	
Race				
White	239	(47)	253	(48)
Black	135	(27)	143	(27)
Asian	19	(4)	23	(4)
Hispanic	56	(11)	50	(10)
Other	61	(12)	58	(11)
Country (number of sites)				
United States (75)	366	(72)	380	(72)
Canada (6)	16	(3)	19	(4)
South Africa (8)	125	(25)	126	(24)
Brazil (3)	3	(1)	2	(<1)

Source: Sponsor table

3.1.4 Statistical Methodologies

The co-primary efficacy analysis was the study outcome with respect to the clinical response of the CE and MITT analysis populations at the post-treatment follow-up visit. Clinical non-inferiority of the two treatments was determined if the lower bound of the two-sided 95% confidence interval (CI) of the difference in proportions of satisfactory outcomes between treatments (meropenem minus imipenem-cilastatin) in the CE and MITT analysis population was greater than –10% using the asymptotic normal approximation to the binomial distribution, without continuity correction, for the difference in proportions. Subgroup analyses were performed based on whether dosages were adjusted for renal function. The analysis of patients with dose adjustments based upon renal function (RDA) was considered a sensitivity analysis. Additional assessments were performed on the CE analysis population at the post-treatment follow-up visit sub-grouped by primary infection diagnosis, age, gender, race, location of study

center, diabetes mellitus, and initial surgical intervention. Concordance between clinical and microbiological outcomes at the
post-treatment follow-up visit in the CE analysis population was also determined.

Secondary analyses were based on data obtained at end-of-treatment and post-treatment follow-up visits for patients in the analysis populations described below (excluding clinical outcomes assessed as co-primary variables): CE, modified intent-to-treat (MITT), ITT, microbiological ITT, microbiological MITT, and fully evaluable (FE). Methods and models were the same as for the primary analysis, and were presented for all patients, patients with RDA, and patients with no adjustment in dosage for renal function (NRDA).

Patients were assigned to the following analysis populations:

Safety analysis population: all patients who received at least 1 dose of study drug were assigned according to the treatment received
ITT analysis population: all patients who received at least 1 dose of study drug were assigned according to the treatment randomized
Microbiological ITT analysis population: all patients in the ITT analysis population with an identified pretreatment pathogen
MITT analysis population: all patients in the ITT analysis population who were hospitalized with a cSSSI and met all study inclusion and exclusion criteria
Microbiological MITT analysis population: all patients in the MITT analysis population with an identified pretreatment pathogen
CE analysis population: all patients in the MITT analysis population who fulfilled all predefined evaluability criteria
FE analysis population: all patients in the CE analysis population with an identified pretreatment pathogen

3.1.5 Results and Conclusions

The study demonstrated the non-inferiority of meropenem (500 mg iv every 8 hours) to imipenem-cilastatin (500mg iv every 8 hours) for the treatment of hospitalized patients with complicated skin and skin structure infections. From the Medical Officer's analysis of the clinically evaluable (CE) population, the proportions of satisfactory outcomes were 85.4% for meropenem versus 81.4% for imipenem, a 4.0% difference in proportions with 95% CI of (-2.2, 10.4). Since the lower bound of this 95% CI is larger than the non-inferiority margin of -10%, this result demonstrated non-inferiority of meropenem to imipenem-cilastatin in the treatment of patients with clinical evidence of complicated skin and skin structure bacterial infection. Non-inferioirty is also demonstrated in the Medical Officer's analysis of the MITT population, the proportions of satisfactory outcomes were 72.4% for meropenem versus 73.5% for imipenem, a

-1.1% difference with a 95% CI (-7.8, 5.6). Efficacy results from the CE and MITT populations are considered co-primary in demonstrating non-inferiority.

Table 3 Clinical outcomes at the post-treatment follow-up visit

Analysis Population	Meropenem			Imipenem			Difference	
	N	n	%	N	n	%	%	95% CI
CE								
Applicant	261	225	86.2	287	238	82.9	3.3	(-2.8, 9.3)[a]
Medical Officer	254	217	85.4	279	227	81.4	4.0	(-2.2, 10.4)
MITT								
Applicant	334	244	73.1	358	268	74.9	-1.8	(-8.4, 4.7)[a]
Medical Officer	323	234	72.4	344	253	73.5	-1.1	(-7.8, 5.6)
FE								
Applicant	209	185	88.5	231	192	83.1	5.4	(-1.1, 11.9)
Medical Officer	209	181	86.6	229	186	81.2	5.4	(-1.5, 12.2)
Microbiological MITT								
Applicant	279	205	73.5	303	225	74.3	-0.8	(-7.9, 6.4)
Medical Officer	274	200	73.0	298	218	73.2	-0.2	(-7.4, 7.1)
Microbiological ITT								
Applicant	404	233	57.7	416	258	62.0	-4.3	(-11.1, 2.4)
Medical Officer	403	232	57.6	415	256	61.7	-4.1	(-10.8, 2.6)
ITT								
Applicant	510	295	57.8	527	325	61.7	-3.8	(-9.8, 2.1)
Medical Officer	510	295	57.8	527	321	60.9	-3.1	(-9.0, 2.9)

[a] Co-primary efficacy analysis, CE Clinically evaluable, CI Confidence interval, FE Fully evaluable, ITT Intention-to-treat, MITT Modified intention-to-treat.

Table 3 presents results from analyses conducted in the co-primary CE and MITT populations as well as secondary populations. Table 3 also includes the Medical Officer's analysis which was conducted due to the re-classification of a few patients with respect to the stated inclusion/exclusion criteria. However, this analysis did not change the overall conclusion of non-inferiority of meropenem (500 mg iv every 8 hours) to imipenem-cilastatin (500mg iv every 8 hours) for treatment of hospitalized patients with complicated skin and skin structure infections.

At the post-treatment follow-up visit, microbiologic outcomes were concordant in 91% of meropenem recipients and 96% of imipenem-cilastatin recipients. The difference between meropenem and imipenem-cilastatin in concordance rates was due to the more frequent persistence of *Staphylococcus aureus* in meropenem patients. Table 4 shows the proportions of patients in these populations with satisfactory microbiologic outcomes at follow-up. No

significant differences were observed between the applicant's and the medical officer's findings. Additionally, there were also no clinically relevant differences in concordance at the end-of-treatment visit. These analyses are consistent with the primary endpoint analyses.

Table 4 Microbiologic outcomes at the post-treatment follow-up visit

Analysis Population	Meropenem			Imipenem			Difference	
	N	n	%	N	n	%	%	95% CI
FE								
Applicant	209	166	79.4	231	183	79.2	0.2	(-7.4, 7.8)
Medical Officer	209	163	78.0	229	178	77.7	0.3	(-7.5, 8.1)
Microbiological MITT								
Applicant	279	182	65.2	303	207	68.3	-3.1	(-10.7, 4.6)
Medical Officer	274	178	65.0	298	201	67.4	-2.4	(-10.3, 5.3)
Microbiological ITT								
Applicant	404	209	51.7	416	236	56.7	-5.0	(-11.8, 1.8)
Medical Officer	403	208	51.6	415	235	56.6	-5.0	(-11.8, 1.8)

[a] Co-primary efficacy analysis, CE Clinically evaluable, CI Confidence interval, FE Fully evaluable, ITT Intention-to-treat, MITT Modified intention-to-treat.

The non-inferiority of meropenem to imipenem-cilastatin is also supported in assessments of subpopulations categorized by dosage adjustment, initial surgical intervention, infection diagnosis, diabetes mellitus, patient age, gender, location of study center, and common pretreatment pathogens. Differences in the proportions of patients with successful microbiological outcomes in secondary analyses of the FE, microbiological MITT, and microbiological ITT populations support the results of the primary analysis of clinical outcome. Among the most common pretreatment pathogens isolated from at least 10 patients in the FE analysis population, there were no clinically relevant differences between treatment groups in the proportion of patients with clinically successful outcomes at either time of assessment. There were no clinically relevant differences between the proportion of patients with satisfactory pretreatment pathogen outcomes and corresponding proportions of patients with satisfactory clinical outcomes.

The proportions of patients who were switched to oral antibiotic therapy were similar between treatment groups in the ITT, MITT, CE, and FE analysis populations. The most common concomitant antibacterial medication administered to at least 5% of patients in either treatment group was vancomycin. One thousand nineteen (98%) patients took concomitant non-antibacterial drugs, 500 (98%) patients randomized to meropenem and 519 (99%) patients randomized to imipenem-cilastatin. The most common concomitant non-antibacterial medications administered by at least 20% of patients in either treatment group were paracetamol

(acetaminophen), morphine, regular insulin, and combination therapy of hydrocodone plus paracetamol. There were no clinically relevant differences in concomitant medications between treatment groups. There were no statistically significant differences between treatment groups in time to hospital discharge for patients in the CE analysis population with satisfactory (unsatisfactory) clinical outcomes; 7.3 (13.2) days for patients randomized to meropenem versus 7.1 (12.2) days for patients randomized to imipenem-cilastatin.

3.2 Safety

Table 5 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety population)

	Meropenem (N=511)		Imipenem-cilastatin (N=526)	
Category of adverse event	**n**	**(%)**	**n**	**(%)**
Any adverse events	297	(58.1)	298	(56.7)
Drug related	46	(9.0)	57	(10.8)
Leading to withdrawal	13	(2.5)	14	(2.7)
Deaths	10	(2.0)	9	(1.7)
Serious adverse events	41	(8.0)	43	(8.2)
Leading to death or immediately life-threatening	14	(2.7)	10	(1.9)
Not leading to death and not life threatening	31	(6.1)	37	(7.0)
Leading to withdrawal	9	(1.8)	6	(1.1)
Drug-related	3	(0.6)	2	(0.4)
Any adverse events	297	(58.1)	298	(56.7)
Drug related	46	(9.0)	57	(10.8)
Leading to withdrawal	13	(2.5)	14	(2.7)
Deaths	10	(2.0)	9	(1.7)
Serious adverse events	41	(8.0)	43	(8.2)
Leading to death or immediately life-threatening	14	(2.7)	10	(1.9)
Not leading to death and not life threatening	31	(6.1)	37	(7.0)
Leading to withdrawal	9	(1.8)	6	(1.1)
Drug-related	3	(0.6)	2	(0.4)
Other significant adverse event	0		0	
	Total number of adverse events			
Any adverse events	920		848	
Drug-related adverse event	60		96	
Serious adverse events not leading to death and not life threatening	46		44	
Drug-related serious adverse events	3		2	

Source: Sponsor table, Patients with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

The number of patients who had adverse events (AEs) or serious adverse events (SAEs) and/or discontinued treatment was similar between the meropenem and imipenem-cilastatin groups as shown in table 5. The number of patients who discontinued study treatment due to a SAE was approximately 1-2 % for each treatment group. The number of patients who died was also similar: meropenem group (10 patients, 2%) versus imipenem-cilastatin group (9 patients, 1.7%).

The most commonly reported AEs (>5% in any group) were headache, nausea, constipation, diarrhea, anemia, pain, and pruritus for either treatment groups. Nausea, constipation and pruritus were reported by a larger proportion of patients in the imipenem-cilastatin group than in the meropenem group (Table 5).

The frequency of AEs was similar across the treatment groups, and the majority of AEs were assessed as mild to moderate in intensity by each investigator. In both treatment groups, less than 11% of the AEs were drug-related as assessed by the investigator; diarrhea was assessed to be drug-related in >2% of patients in both groups. In general across the treatment groups, the majority of the AEs occurred during the iv treatment phase. A similar trend was observed in either treatment groups for drug-related AEs.

There were no consistent patterns in AE incidence by age, gender, race or renal impairment across the treatment groups. The majority of the patients did not require renal dose adjustment for either treatment groups (927 of 1037 patients). Almost twice as many patients in the imipenem-cilastatin group (74 patients) required renal dose adjustment at the beginning of the study compared to the meropenem group (46 patients). This is because dose adjustment is required at a higher creatinine clearance for patients treated with imipenem-cilastatin.

Table 6 Number (%) of subjects with the most commonly reported (5% in any treatment group) adverse events, sorted by decreasing order of frequency groups (safety population)

	Meropenem (N=511)		Imipenem-cilastatin (N=526)	
COSTART Preferred term	n	(%)	n	(%)
Headache	40	(7.8)	33	(6.3)
Nausea	40	(7.8)	57	(10.8)
Constipation	36	(7.1)	44	(8.4)
Diarrhea	36	(7.0)	32	(6.1)
Anemia	28	(5.5)	21	(4.0)
Pain	26	(5.1)	20	(3.8)
Pruritus	25	(4.9)	31	(5.9)

Source: Sponsor table
Common adverse events: Adverse events occurring at an incidence of 5% in any treatment group.
Patients with multiple events in the same category are counted only once in that category.
Patients with multiple events in more than one category are counted once in each of those categories.

The overall information from the laboratory results did not raise any safety concern for the use of meropenem for the treatment of hospitalized patients with complicated skin and skin structure infections. In general, meropenem (500 mg iv every 8 hours) provides adequate safety, tolerability and efficacy in the treatment of hospitalized patients with complicated skin and skin structure bacterial infections.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

At the post-treatment follow-up visit in the MITT and CE populations, there were no clinically relevant differences in the proportions of satisfactory outcomes between treatment groups based on age, gender, race (table 7). In the CE population, Meropenem showed higher success rates in patients who were black (96.0% versus 88.5%) and patients who were 65 or older (81.4% versus 71.7%), however these differences were not statistically significant.

Table 7 Number (%) of patients with successful clinical outcomes by patient Age, Gender, Race for Post-treatment follow-up visit (MITT and CE analysis populations)

	Meropenem (MITT Population)	Imipenem-cilastatin (MITT Population)	Meropenem (CE Population)	Imipenem-cilastatin (CE Population)
	% (n/N)	% (n/N)	% (n/N)	% (n/N)
All patients	73.1 (244/334)	74.9 (268/358)	86.2 (225/261)	82.9 (238/287)
Age, years				
<65	72.7 (202/278)	76.1 (229/301)	87.2 (190/218)	85.1 (205/241)
≥65	75.0 (42/56)	68.4 (39/57)	81.4 (35/43)	71.7 (33/46)
≥75	78.3 (18/23)	65.4 (17/26)	83.3 (15/18)	68.4 (13/19)
Gender				
Male	71.4 (140/196)	69.7 (154/221)	87.8 (130/148)	79.7 (37/172)
Female	75.4 (104/139)	83.2 (114/137)	84.1 (95/113)	87.8 (101/115)
Race				
White	63.2 (86/136)	69.5 (114/164)	75.0 (78/104)	76.5 (101/132)
Black	79.4 (77/97)	80.0 (85/105)	96.0 (72/75)	88.5 (77/87)
Asian	87.5 (14/16)	77.8 (14/18)	86.7 (13/15)	87.5 (14/16)
Hispanic	76.9 (30/39)	82.1 (23/28)	90.0 (27/30)	93.8 (15/16)
Other	80.4 (37/46)	76.7 (33/43)	94.6 (35/37)	86.1 (31/36)

Source: Derived from Sponsor tables

4.2 Other Special/Subgroup Populations

Additionally, no clinically relevant differences between treatment groups were found in the MITT and CE groups with respect to the other factors such as geographic region, diabetes mellitus, pre-treatment antibiotics, renal dose adjustment (table 8).

Table 8 Number (%) of patients with successful clinical outcomes by other patient factors, Post treatment follow-up visit (MITT and CE analysis populations)

	Meropenem (MITT Population)	Imipenem-cilastatin (MITT Population)	Meropenem (CE Population)	Imipenem-cilastatin (CE Population)
	% (n/N)	% (n/N)	% (n/N)	% (n/N)
All patients	73.1 (244/334)	74.9 (268/358)	86.2 (225/261)	82.9 (238/287)
Geographic Region				
US	67.1 (143/213)	70.0 (161/230)	80.0 (132/165)	77.9 (134/172)
Non-US	83.5 (101/121)	83.6 (106/128)	96.9 (93/96)	90.4 (104/115)
Diabetes Mellitus				
Diabetic	73.0 (89/122)	66.1 (87/124)	85.6 (83/97)	72.4 (76/105)
Non-diabetic	73.1 (155/212)	79.7(184/231)	86.6 (142/164)	89.0 (162/182)
Pre-treatment Antibiotics				
With	69.5 (141/203)	67.3 (150/223)	83.3 (130/156)	77.4 (127/164)
Without	78.6 (103/131)	87.4 (118/135)	90.5 (95/105)	90.2 (111/123)
Renal Dose Adjustment				
RDA	67.9 (19/28)	67.4 (31/46)	87.5 (210/240)	84.2 (213/253)
NRDA	73.5 (225/306)	76.0 (237/312)	71.5 (15/21)	73.5 (25/34)

Source: Derived from Sponsor tables

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Non-inferiority of meropenem to imipenem-cilastatin was demonstrated within the acceptable margin of -10% in the CE and MITT co-primary populations. No clinically relevant differences in cure rates were observed between meropenem and imipenem-cilastatin with respect to various covariates that included primary infection diagnosis, common pretreatment pathogens, age, gender and race. The analyses of the microbiological outcome at the EOT and FU visits in the microbiologically documented infections (FE, microbiological MITT, and microbiological

ITT) are also consistent with the conclusion of non-inferiority of meropenem to imipenem-cilastatin for cSSSIs caused by *Staphylococcus aureus* (methicillin susceptible strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *viridans* group *streptococci*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species.

5.2 Conclusions and Recommendations

This study demonstrates the non-inferiority of meropenem to imipenem-cilastatin in the treatment of patients with clinical evidence of complicated skin and skin structure bacterial infections caused by susceptible pathogens. Meropenem, 500 mg iv q8h in adults, is safe and effective therapy for patients treated for complicated SSSI due to *Staphylococcus aureus* (methicillin susceptible strains), *Streptococcus pyogenes*, *Streptococcus agalactiae, viridans* group *streptococci*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species.

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/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-706 / S-018

MICROBIOLOGY REVIEW

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
Clinical Microbiological Review of Efficacy Supplement

NDA#: 50-706 **REVIEW #:** 1 **COMPLETED DATE:** 05/19/05

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
50-706/SE1-018	07/28/04	07/28/04	07/28/04
50-706/SE1-018 (BI)	02/16/05	02/17/05	03/14/05

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SUBMISSIONS REVIEWED:

1. The efficacy supplemental application, sNDA 50-706/SE1-018, dated 07/28/04, provides data for the use of meropenem, 500 mg IV every 8 hours, as treatment for patients with complicated skin and skin structure infections (cSSSI) due to *Staphylococcus aureus* (methicillin susceptible isolates), *Streptococcus pyogenes, Streptococcus agalactiae,* viridans group streptococci, *Enterococcus faecalis, Pseudomonas aeruginosa, Escherichia coli,* [redacted] *Proteus mirabilis, Bacteroides fragilis,* [redacted] and *Peptostreptococcus* species, respectively

2. The "efficacy" Supplemental amendment, NDA 50-706/SEI-018 (BI), dated 02/16/05, contains the Applicant's response to the FDA Clinical Microbiology Reviewer's questions.

DRUG PRODUCT NAME:

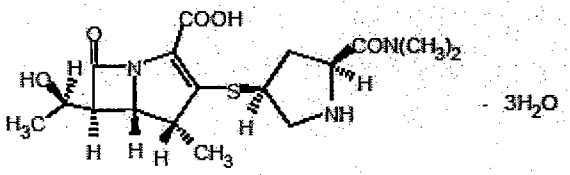
Proprietary:	MERREM® I.V. (meropenem for injection)
Nonproprietary/USAN:	meropenem
Code Names/#'s:	ICI 194,660 - SM 7338; MERO-R, ZD3591
INN: Meropenem	USAN: Meropenem

CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA, MOL. WT. (meropenem):

Chemical Name:

(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

Structural Formula:



Molecular Formula	=	$C_{17}H_{25}N_3O_5S.3H_2O$
Molecular Weight	=	437.52

DOSAGE FORM: Crystalline powder (in vials) to be reconstituted (becoming a solution); Injection.

STRENGTH: Each vial contains either 500 mg or 1 g meropenem to be reconstituted.

ROUTE OF ADMINISTRATION: "For Intravenous Use Only"

DISPENSED: _x_ Rx

PHARMACOLOGICAL CATEGORY: Carbapenem antibiotic.

APPROVED INDICATION(s):

Intra-abdominal Infections: Complicated appendicitis and peritonitis caused by viridans group streptococci, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *B. thetaiotaomicron*, and *Peptostreptococcus* species.

Bacterial Meningitis (Pediatric patients ≥ 3 months only): Bacterial meningitis caused by *Streptococcus pneumoniae*‡, *Haemophilus influenzae* (β-lactamase and non-β-lactamase-producing strains), and *Neisseria meningitidis.*

‡ The efficacy of meropenem as monotherapy in the treatment of meningitis caused by penicillin non-susceptible strains 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

PRECAUTIONS - Pediatrics, **ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION** sections.
Appropriate cultures should usually be performed before initiating antimicrobial treatment in order to isolate and identify the organisms causing infection and determine their susceptibility to MERREM I.V.

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

Antimicrobial therapy should be adjusted, if appropriate, once the results of culture(s) and antimicrobial susceptibility testing are known.

RELATED DOCUMENTS:

[ ] 96.

REMARKS / COMMENTS:

This is a Clinical Microbiology Review on the efficacy supplemental application, sNDA 50-706/SE1-018. The Supplement contains data for the proposed use of meropenem, 500 mg IV every 8 hours, as treatment for patients with complicated skin and skin structure infections (cSSSI) due to *Staphylococcus aureus* (methicillin susceptible isolates), *Streptococcus pyogenes, Streptococcus agalactiae,* viridans group streptococci. *Enterococcus faecalis, Pseudomonas aeruginosa, Escherichia coli,* [redacted] *roteus mirabilis, Bacteroides fragilis* [redacted] nd *Peptostreptococcus* species, respectively

CONCLUSIONS:

The Clinical Microbiology Reviewer recommends "approval" for NDA 50-706/SE1-018.

From the Clinical Microbiology Reviewer's perspective, the clinical microbiological data on NDA 50-706/SE1-018 for the treatment of complicated skin and skin structure infections (cSSSI)

[ ]

NOTE: Microbiologically, the following microbial nomenclatures are not permitted into the "1st List of Microorganisms" (the "*in vivo*" list) of the Package Insert for the treatment of cSSSI:

Klebsiella species
Prevotella species

Clinical Study 3591L0079 -- "A Multicenter, Randomized, Double-blind, Comparative Trial of Intravenous MERREM™ (meropenem, ICI 194,660) vs. PRIMAXIN® I.V. (imipenem-cilastatin) in the Treatment of Hospitalized Subjects with Complicated Skin and Skin Structure Infections."

Analyses were done on the number and percentage of patients with satisfactory clinical, microbiological, and pretreatment pathogen outcomes for the proposed targeted organisms at the "post-treatment follow-up visit" (Fully Evaluable analysis set).

A. Clinical Microbiology

1. The following is a summary of the microbiological eradication rates on the aforementioned Fully Evaluable (FE) population for Clinical Study 3591L0079:

   Staphylococcus aureus (methicillin susceptible) for meropenem is 78.4% (69/88 isolates eradicated) and for imipenem-cilastatin it is 83% (83/100 isolates eradicated);

   Enterococcus faecalis for meropenem is 75% (9/12 isolates eradicated) and for imipenem-cilastatin it is 65% (13 isolates eradicated).

   [ ]

   Proteus mirabilis for meropenem is 84.6% (11/13 isolates eradicated) and for imipenem-cilastatin it is 71.4% (5/7 isolates eradicated).

   Peptostreptococcus species for meropenem is 81.3% (13/16 isolates eradicated) and for imipenem-cilastatin it is 85.7 (18/21 isolates eradicated). Microbiologically, for this particular bacterial labeling nomerclature, "*Peptostreptococcus* species" is permitted in the PI labeling.

   [ ]

2. There is no data on meropenem activity against community-acquired or hospital-acquired methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* that harbor or express the Panton-Valentine leucocidin gene(s)."

B. Package Insert Labeling

The "approval" letter should be issued to the Applicant, after negotiation of their proposed "draft" labeling for sNDA 50-706/SEI-018 for the use of MERREM® IV for the management of Complicated Skin and Skin Structure Infection. This includes all the Agency's labeling recommendations, and some informational, in the **MICROBIOLOGY** section, ***Susceptibility Test Methods*** subsection, and **REFERENCES** section of the Package Insert labeling. The changes and informational comments are found on pages 52 to 63 and finalized at the end of this review on pages 65 to 71.

EXECUTIVE SUMMARY

NDA 50-706 / SE1-018

AstraZeneca UK Limited / AstraZeneca Pharmaceuticals LP (AstraZeneca)

MERREM® I.V. (meropenem for injection)

INTRODUCTION

The Applicant submits the efficacy supplemental application, sNDA 50-706/SE1-018, providing data for the proposed use of meropenem, 500 mg IV every 8 hours, as treatment for patients with complicated skin and skin structure infections (cSSSI) due to *Staphylococcus aureus* (methicillin susceptible strains), *Streptococcus pyogenes, Streptococcus agalactiae,* viridans group streptococci, *Enterococcus faecalis, Pseudomonas aeruginosa, Escherichia coli,* *Proteus mirabilis, Bacteroides fragilis,* and *Peptostreptococcus* species, respectively .

Meropenem belongs to the ß-lactam class of antibiotics, specifically the carbapenems, which possess a broad antibacterial spectrum.

Meropenem is stable to dehydropeptidase (DHP-1), an enzyme in renal tubular cells that causes extensive metabolism of carbapenems. Unlike imipenem, meropenem is stable to human DHP-1 and thus does not require co-administration with cilastatin [1] in order to inhibit renal metabolism and consequent nephrotoxicity.

Complicated skin and skin structure infections (cSSSI) include complicated cellulitis, complex abscesses, perirectal abscesses, surgical and traumatic wound infections, infected diabetic and ischemic ulcers, and other significant bacterial skin infections that require hospitalization, surgical intervention, and parenteral antibiotic therapy (FDA 1998).

Complicated cellulitis can be defined as cellulitis occurring in the setting of diabetes mellitus or cellulitis requiring a surgical intervention or cellulitis in conjunction with evidence of deeper soft tissue involvement, bacteremia, or involvement of the perineal or perirectal areas.

In contrast to uncomplicated skin infections such as impetigo, erysipelas, and folliculitis, complicated skin and skin structure infections may be polymicrobial and often involve rapidly growing Gram-negative and anaerobic pathogens in addition to ß-hemolytic streptococci and *Staphylococcus aureus* [2, 3, 4]. Furthermore, complicated skin and skin structure infections frequently involve deeper tissue layers, may be more rapidly progressive, and pose greater risk of systemic spread and tissue loss than uncomplicated infections [3]. As a result, management of complicated skin and skin structure infections frequently requires hospitalization and parenteral antibiotic therapy, and may require surgical drainage and/or debridement. Given the range of potential pathogens, broad-spectrum antibiotic therapy is frequently indicated for management of these infections [2, 3].

The choice of antibiotic therapy has been further complicated by the rapid emergence of antimicrobial resistance in potential Gram-positive and Gram-negative skin and skin structure pathogens [5, 6]. Effective antibacterial agents are required in order to continue to provide adequate treatment for patients with complicated skin and skin structure infections.

PRECLINICAL EFFICACY (*IN VITRO*)

Mechanism of Action

Meropenem exerts its action by penetrating bacterial cells readily and interfering with the synthesis of vital cell wall components, which leads to cell death.

Antimicrobial Spectrum of Activity

Meropenem is more active in vitro against *Pseudomonas aeruginosa,* a potential cause of complicated skin and skin structure infections (cSSSI), than ertapenem, the third carbapenem approved for use in the United States

In vitro studies demonstrate that meropenem has a broad spectrum of activity against most clinically important Gram-positive and Gram-negative aerobic organisms, including α- and ß-hemolytic streptococci, methicillin-susceptible *Staphylococcus aureus*, *Enterococcus faecalis*, enteric Gram-negative bacilli, and *Pseudomonas aeruginosa*. Activity against anaerobes, including *Bacteroides*, *Clostridium*, and *Peptostreptococcus* species, also is demonstrated [7, 8, 9].

As demonstrated for other penicillin, cephalosporin, and carbapenem antibiotics, meropenem is not clinically active against methicillin-resistant *Staphylococcus aureus*. Pharmacokinetic studies have demonstrated penetration of meropenem into interstitial tissue fluid, including skin blister fluid [10, 11].

Bactericidal Activity

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.

Resistance

a. 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 penicillin binding proteins (PBP), 3) increased expression of efflux pump components, and 4) production of antibiotic-destroying enzymes (carbapenemases, metallo-β-lactamases) [12].

b. Cross-Resistance

Cross resistance is sometimes observed with strains resistant to other carbapenems.

CLINICAL MICROBIOLOGY RESULTS for CLINICAL STUDY 3591L0079

The following is a summary of clinical response, microbiological response, and pretreatment pathogen response for all pretreatment pathogens. Clinical and Clinical Microbiology outcomes for the proposed targeted pathogens are shown, as follows:

The following **Table**[*] shows the number and percentage of patients with satisfactory clinical, microbiological, and pretreatment pathogen outcomes for the proposed targeted organisms at the "post-treatment follow-up visit" (Fully Evaluable analysis set).

Pathogen Class	Meropenem							Imipenem-cilastatin						
Pathogen[a]		Satisfactory Clinical Outcomes		Satisfactory microbiological outcomes		Satisfactory pretreatment pathogen outcomes			Satisfactory Clinical Outcomes		Satisfactory microbiological outcomes		Satisfactory pretreatment pathogen outcomes	
	N	n	%	n	%	n	%	N	n	%	n	%	n	%
Gram-positive aerobes														
Staphylococcus aureus: methicillin susceptible	88	82	93.2	68	77.3	69	78.4	100	84	84.0	80	80.0	83	83.0
Streptococcus pyogenes (Group A)	29	26	89.7	26	89.7	27	93.1	32	28	87.5	27	84.4	29	90.6
Streptococcus agalactiae (Group B)	17	12	70.6	10	58.8	14	82.4	19	16	84.2	14	73.7	16	84.2
Enterococcus faecalis	12	9	75.0	8	66.7	9	75.0	20	14	70.0	13	65.0	13	65.0
Streptococcus viridans Group, nos	12	11	91.7	11	91.7	11	91.7	6	5	83.3	5	83.3	5	83.3
Gram-negative aerobes														
Escherichia coli	15	12	80.0	12	80.0	12	80.0	21	15	71.4	13	61.9	14	66.7
Pseudomonas aeruginosa	15	11	73.3	10	66.7	10	66.7	15	13	86.7	13	86.7	14	93.3
Proteus mirabilis	13	11	84.6	9	69.2	11	84.6	7	6	85.7	4	57.1	5	71.4
Anaerobes														
Bacteroides fragilis	11	10	90.9	10	90.9	10	90.9	10	9	90.0	8	80.0	9	90.0
Peptostreptococcus species[c]	16	13	81.3	13	81.3	13	81.3	21	18	85.7	18	85.7	18	85.7

[*] Adapted from eNDA 50-706/SE1-018, eDocument 2671924, AstraZeneca, Study Code: 3591IL0079, Table 2, Dated: 02/16/05. Data adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, Table 11.2.4.1, Table 11.2.4.2, and Table 11.2.4.3, Pages 830 to 953, Dated: 07/28/04.

[a] Patients may have more than one pretreatment pathogen.

[c] *P. magnus*, *P. micros*, *P. species*, *P. prevotii*, *P. anaerobius*, and *P. asaccharolyticus*

nos Not otherwise specified

1. The following is a summary of the microbiological eradication rates on the Fully Evaluable (FE) population for the aforementioned Table, Clinical Study 3591L0079:

   Staphylococcus aureus (methicillin susceptible) for meropenem is 78.4% (69/88 isolates) and for imipenem-cilastatin it is 83% (83/100 isolates);

   Enterococcus faecalis for meropenem is 75% (9/12 isolates) and for imipenem-cilastatin it is 65% (13 isolates).

   [ ]

   Proteus mirabilis for meropenem is 84.6% (11/13 isolates) and for imipenem-cilastatin it is 71.4% (5/7 isolates).

   Peptostreptococcus species for meropenem is 81.3% (13/16 isolates) and for imipenem-cilastatin it is 85.7 (18/21 isolates). Microbiologically, for this particular bacterial labeling nomerclature, "*Peptostreptococcus* species", is permitted in the PI labeling.

   [ ]

2. There is no data on meropenem activity against community-acquired or hospital-acquired methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* that harbor or express the Panton-Valentine leucocidin gene(s)."

CONCLUSIONS

The Clinical Microbiology Reviewer recommends "approval" for NDA 50-706/SE1-018.

From the Clinical Microbiology Reviewer's perspective, the clinical microbiological data on NDA 50-706/SE1-018 for the treatment of complicated skin and skin structure infections (cSSSI) due to *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus pyogenes, Streptococcus agalactiae,* viridans group streptococci, *Enterococcus faecalis* (excluding vancomycin-resistant isolates), *Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Bacteroides fragilis* and *Peptostreptococcus* species are satisfactory.

The "approval" letter should be issued to the Applicant, after negotiation of their proposed "draft" labeling for sNDA 50-706/SEI-018 for the use of MERREM® IV for the management of Complicated Skin and Skin Structure Infection. This includes all the Agency's labeling recommendations, and some informational, in the **MICROBIOLOGY** section, ***Susceptibility Test Methods*** subsection, and **REFERENCES** section of the Package Insert labeling. The changes and informational comments are found on pages 52 to 63 and finalized at the end of this review on pages 65 to 71.

NOTE: Microbiologically, the following microbial nomenclatures are not permitted into the "1st List of Microorganisms" (the "*in vivo*" list) of the Package Insert for the treatment of cSSSI:

species and *Prevotella* species.

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I. INTRODUCTION

The Applicant submits the efficacy supplemental application, sNDA 50-706/SE1-018, providing data for the proposed use of meropenem, 500 mg IV every 8 hours, as treatment for patients with complicated skin and skin structure infections (cSSSI) due to *Staphylococcus aureus*

[ ]

Meropenem belongs to the ß-lactam class of antibiotics, specifically the carbapenems, which possess a broad antibacterial spectrum.

Meropenem is stable to dehydropeptidase (DHP-1), an enzyme in renal tubular cells that causes extensive metabolism of carbapenems. Unlike imipenem, meropenem is stable to human DHP-1 and thus does not require co-administration with cilastatin [1] in order to inhibit renal metabolism and consequent nephrotoxicity.

Complicated skin and skin structure infections (cSSSI) include complicated cellulitis, complex abscesses, perirectal abscesses, surgical and traumatic wound infections, infected diabetic and ischemic ulcers, and other significant bacterial skin infections that require hospitalization, surgical intervention, and parenteral antibiotic therapy (FDA 1998). Complicated cellulitis can be defined as cellulitis occurring in the setting of diabetes mellitus or cellulitis requiring a surgical intervention or cellulitis in conjunction with evidence of deeper soft tissue involvement, bacteremia, or involvement of the perineal or perirectal areas. In contrast to uncomplicated skin infections such as impetigo, erysipelas, and folliculitis, complicated skin and skin structure infections may be polymicrobial and often involve rapidly growing Gram-negative and anaerobic pathogens in addition to ß-hemolytic streptococci and *Staphylococcus aureus* [2, 3, 4]. Furthermore, complicated skin and skin structure infections frequently involve deeper tissue layers, may be more rapidly progressive, and pose greater risk of systemic spread and tissue loss than uncomplicated infections [3]. As a result, management of complicated skin and skin structure infections frequently requires hospitalization and parenteral antibiotic therapy, and may require surgical drainage and/or debridement. Given the range of potential pathogens, broad-spectrum antibiotic therapy is frequently indicated for management of these infections [2, 3].

The choice of antibiotic therapy has been further complicated by the rapid emergence of antimicrobial resistance in potential Gram-positive and Gram-negative skin and skin structure pathogens [5, 6]. Effective antibacterial agents are required in order to continue to provide adequate treatment for patients with complicated skin and skin structure infections.

II. PRECLINICAL EFFICACY (*IN VITRO*)

A. Mechanism of Action

Meropenem exerts its action by penetrating bacterial cells readily and interfering with the synthesis of vital cell wall components, which leads to cell death.

B. Antimicrobial Spectrum of Activity

Meropenem is more active *in vitro* against *Pseudomonas aeruginosa,* a potential cause of complicated skin and skin structure infections (cSSSI), than ertapenem, the third carbapenem approved for use in the United States

In vitro studies demonstrate that meropenem has a broad spectrum of activity against most clinically important Gram-positive and Gram-negative aerobic organisms, including α- and ß-hemolytic streptococci, methicillin-susceptible *Staphylococcus aureus*, *Enterococcus faecalis*, enteric Gram-negative bacilli, and *Pseudomonas aeruginosa*. Activity against anaerobes, including *Bacteroides*, *Clostridium*, and *Peptostreptococcus* species, also is demonstrated [7, 8, 9].

As demonstrated for other penicillin, cephalosporin, and carbapenem antibiotics, meropenem is not clinically active against methicillin-resistant *Staphylococcus aureus*. Pharmacokinetic studies have demonstrated penetration of meropenem into interstitial tissue fluid, including skin blister fluid [10, 11].

C. Bactericidal Activity

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 [redacted] against which lethal activity is not observed.

D. Resistance

1. Mechanism of Resistance

There are several mechanisms of resistance to carbapenems: a) decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) causing reduced bacterial uptake, b) reduced affinity of the target penicillin binding proteins (PBP), c) increased expression of efflux pump components, and d) production of antibiotic-destroying enzymes (carbapenemases, metallo-β-lactamases) [12].

2. Cross-Resistance

Cross resistance is sometimes observed with strains resistant to other carbapenems.

III. CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

A. Clinical Study 3591L0079

NAME & ADDRESS OF APPLICANT:

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Alderley Park,
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US NAME & ADDRESS OF AGENT:

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PO Box 8355
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Tel: (302) 886-8016
FAX: (302) 886-2822

Contract Research Organization (CRO):

[ ]

Other Participants:

Non-applicant organizations or individuals

[ ]

Sharon Sherer: Microbiology Project Manager
Paul OeFinger: Microbiology Manager
June Luo: Technical Microbiologist
Karen Heier: Account Executive

Rationale for study design and outcome variables

The proposed clinical study 3591L0079 (cSSSI)is designed and conducted as a multicenter, randomized, double-blind study in full compliance with the recommendations of the FDA Draft Guidance (1998). The
initial design of this study, all subsequent amendments, and the Statistical Analysis Plan have been previously reviewed and agreed with the FDA.

Rationale for drug dose and control groups

Given the range of potential pathogens, broad-spectrum antibiotic therapy is frequently indicated for management of complicated skin and skin structure infections. The choice of antibiotic therapy has been further complicated by the rapid emergence of antimicrobial resistance in potential Gram-positive and Gram-negative skin and skin structure pathogens. Effective antibacterial agents are required in order to continue to provide adequate treatment for patients with complicated skin and skin structure infections.

Protocol Title:

"A Multicenter, Randomized, Double-blind, Comparative Trial of Intravenous MERREM™ (meropenem, ICI 194,660) vs. PRIMAXIN® I.V. (imipenem-cilastatin) in the Treatment of Hospitalized Subjects with Complicated Skin and Skin Structure Infections."

Study Code: 3591L0079

Study Report: May 28, 2004

Study Drugs:

MERREM® (meropenem for injection) I.V: Merrem (ZD3591; meropenem) is a trademark of the AstraZeneca group of companies; and

Primaxin I.V. (Imipenem-cilastatin) is a trademark, the property of Merck & Co, Inc, West Point, PA.

Study Centers:

This study was originally conducted at 75 centers in the United States and 8 centers in South Africa, 6 centers in Canada, and 3 centers in Brazil.

Later, 06/12/02, the number of participating centers are increased to 100 domestic and international centers from 45 to 60 medical centers.

Study Dates:

First patient enrolled: March 28, 2001; and
Last patient completed: December 10, 2003

Study Objectives:

The primary objective of this study is to demonstrate the therapeutic noninferiority of meropenem (500 mg intravenous [IV] every 8 hours) to imipenem-cilastatin (500 mg IV every 8 hours) in hospitalized patients with complicated skin and skin structure infections.

The secondary objective of this study is to assess the safety and tolerability of meropenem (500 mg IV every 8 hours) administered in hospitalized patients with complicated skin and skin structure infections.

Study Design:

This is a multicenter, randomized, double blind, comparative study of IV meropenem and imipenem-cilastatin for the treatment of cSSSI.

Microbiology Inclusion Criteria:

1. Patients are hospitalized males and females, aged 13 years or older, with clinical evidence of complicated skin and skin structure bacterial infection with material suitable for culture from 1 primary site of infection.

   (The eligibility of patients with multiple sites of infection was discussed with AstraZeneca or AstraZeneca's Agents Medical Monitor [Vladimir Mosailov, MD] prior to enrollment. Patients with multiple infected sites are eligible, provided that all pathogens from each infected site are susceptible to both study drugs therapies. The most extensive site of infection is designated as primary and is used for determining microbiological, clinical, and pretreatment pathogen response assessments).

2. Within 72 hours before enrollment, the patient provided an appropriate specimen for culture and susceptibility testing by one of the following methods:

   - a leading edge aspiration culture is obtained for patients with cellulitis in the setting of underlying immunosuppressive disorder or a significant underlying disease that complicated the response to therapy (i.e., diabetes, obesity, mild to moderate peripheral vascular disease, peripheral edema, malnutrition, substance abuse). Two blood cultures are taken from 2 different sites or, if taken from the same site, there must be at least 30 minutes. If blood cultures are positive, they are repeated if clinically indicated every 48 hours until no growth.

   - biopsy, needle aspiration, surgically obtained specimens or deep swabs of fluids/pus from subjects with any of the following infections: complex abscess, perirectal abscess, wound infections, infected ischemic/diabetic ulcers, and infections requiring significant surgical intervention. Surface swabs of open wounds are not acceptable. Samples for anaerobic cultures are immediately transferred into an anaerobic transport system. Specimens are sent for Gram stain, and for aerobic, anaerobic, mycobacterial, and fungal cultures and susceptibility testing on isolated pathogens. Two blood cultures are taken from 2 different sites or, if taken from the same site, at a minimum time interval of 30 minutes. If blood cultures are positive, they are repeated if clinically indicated every 48 hours until no growth.

   - all pretherapy pathogens were susceptible according to agar disk diffusion or MIC dilution testing methods to meropenem, imipenem, and any potential follow-up oral antibiotic.

3. Patients are allowed to enroll before obtaining culture results. Patients who are given more than 24 hours of prior antibacterial therapy within 14 days of study entry are eligible to remain in this study only if a culture demonstrates a persistent pathogen in blood or at the site of infection. Patients who receive 24 hours or less of antibacterial therapy before study entry are considered evaluable even if the culture obtained at study entry reveals no growth. However, if a culture indicates a no growth result, the patient is considered non-evaluable if given more than 24 hours of antecedent antibiotic therapy. For all patients, no antibiotic therapy is allowed after the entry culture is obtained and before the initiation of study therapy.

Microbiology Exclusion Criteria

1. Patients who receive an investigational drug or who use an investigational device within 30 days before entering the study.

2. Patients who are likely to receive other systemic antibiotics during the study.

3. Patients with infections that have a high cure rate after surgical incision alone or with aggressive local wound care (e.g., furuncle or paronychia).

4. Patients with another focus of infection requiring concurrent antibiotics that would interfere with evaluation of the responses to the study drug.

5. Patients with severe peripheral vascular disease likely to require amputation of a body part, which would preclude evaluation of clinical and microbiological response.

6. Patients with infected prosthetic materials (i.e., central venous catheter or dialysis catheter tunnel infections).

Microbiology Restrictions

1. No antibiotic therapy is allowed after the entry culture is obtained and before the infusion of study therapy.

2. Systemically absorbed antibacterial agents or investigational drugs are prohibited during the study except for oral vancomycin, which is allowed to treat patients with suspected or confirmed pseudomembranous colitis caused by *Clostridium difficile*. If another antibacterial regimen is required to treat a patient with a skin and skin structure infection, the study drug is discontinued before the alternate antibiotic is administered and post-treatment procedures are performed.

Treatments

Investigational products:

Table 1* shows the details of the investigational product and other study treatments.

Investigational product or other treatment	Dosage form and strength	Manufacturer	Formulation number	Batch number
Meropenem[a]	powder, 500 mg/20-mL vial	AstraZeneca (Newark, Delaware)	F7145	3345C/ 2000012670 3764C/ 2000012663 8071F/ 2000034348 8071F/ 2000030524 8071F/ 2000033714 8071F/ 2000042002 5526J/ 2000044037 5521J/ 2000045609
Imipenem-cilastatin	powder, 500 mg/10-mL vial	Merck and Company, Inc.	F12843	4475M/ 2000034712 3631M/ 2000037946 4304L/ 2000030525 3811K/ 2000014524 3573N/ 2000045611 4445M/ 2000033762 3703M/ 2000042003
Imipenem-cilastatin	suspension, 500 mg/100 mL	Merck and Company, Inc.	F10021	3582K/ 2000012672

* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 5.4. Treatments, Table 2, Page 38, Dated: 07/28/04.

[a] Meropenem infusion vials (500 mg/100 mL) are not supplied to study centers.

AstraZeneca provided the commercially labeled and packaged meropenem and imipenem-cilastatin.

Constitution of Meropenem for Intravenous Administration

Contents of an IV infusion vial (500 mg/100 mL) are directly constituted with a compatible infusion fluid with agitation to insure complete mixing. Alternatively, contents of an injection vial (500 mg/20 mL) are constituted with sterile water, added to an IV container, and further diluted with an appropriate infusion fluid.

Constitution of Imipenem-Cilastatin for Intravenous Administration

Contents of the imipenem-cilastatin vials or infusion bottles are suspended and transferred to a 100 mL sterile 0.9% (physiological) saline infusion container.

Doses and Treatment Regimens

All study drug therapies are prepared and kept blinded by the pharmacy. Both study drugs are to be administered in an IV bag labeled with dose number, scheduled time of infusion, patient initials, and study number. Each bag is to clearly indicate that this is an investigational drug.

Meropenem

Meropenem is administered by IV infusion over approximately 20 to 30 minutes. The dose and/or frequency of administration is adjusted according to creatinine clearance.

Imipenem-cilastatin

Imipenem-cilastatin is administered by IV infusion over approximately 20 to 30 minutes. The dose and/or frequency of administration is adjusted according to creatinine clearance.

Investigational Product and Comparators / Dosage / Mode of Administration:

AstraZeneca provided commercially labeled and packaged meropenem and imipenem-cilastatin, as follows:

Meropenem powder, 500 mg / 20-mL vial; and

Imipenem-cilastatin powder, 500 mg/10-mL vial and imipenem-cilastatin suspension, 500 mg /100 mL.

Administration by IV infusion over approximately 20 to 30 minutes. The dose and/or frequency of administration is adjusted from 500 mg every 8 hours according to creatinine clearance (>50mL/min for patients randomized to meropenem, >70 mL/min for patients randomized to imipenem-cilastatin).

Target Patient Population

Hospitalized male and female patients with clinical evidence of complicated skin and skin structure bacterial infection with material suitable for culture.

Sample Size

Approximately 1000 hospitalized male and female patients are required to be randomized to study drug in order to acquire 201 clinically evaluable patients in each treatment group.

Gender / Age

Male and Female patients aged 13 years or older.

Duration of Treatment

The duration of IV study treatment is expected to be from 3 to14 days.

Criteria for Evaluation (main variables)

- **Efficacy**

Primary Variable

Clinical outcome at the post-treatment follow-up visit.

The primary variable is the clinical response at the post-treatment follow-up visit. Clinical response is to be based on the investigator's assessment of the course of the skin and skin structure infection. For patients with multiple sites of skin and skin structure infections, the most extensive site of infection is to be designated as primary and is to be used for determining the microbiological, clinical, and pretreatment pathogen response assessments.

Secondary Variables

Clinical outcome at the post-treatment follow-up visit (excluding clinical outcomes assessed as co-primary variables);

Clinical outcome at the end-of-treatment visit;

Microbiological outcome at the end-of-treatment and post-treatment follow-up visits; and

Pretreatment pathogen outcome at the end-of-treatment and the post-treatment follow-up visits.

Additional Heath Economics Variables (informational)

Total length of hospital stay;

Number of IV treatment doses;

Number of days of IV therapy;

Number of days of oral antibiotic therapy; and

Number of intensive care unit bed days- number of days missed from work, school, and other activities since end of IV therapy.

Statistical Methods

The co-Primary efficacy analysis is the study outcome with respect to the clinical response of the CE and MITT analysis sets at the post-treatment follow-up visit.

Secondary analyses are based on data obtained at end-of-treatment and post-treatment follow-up visits for patients in the analysis sets described below (excluding clinical outcomes assessed as co-primary variables):

CE, MITT, intention-to-treat (ITT), microbiological ITT, Microbiological MITT, and Fully evaluable (FE), respectively.

Patients are assigned to the Following Analysis Sets

- Safety Analysis Set All patients who receive at least 1 dose of study drug are assigned according to the treatment received.

- ITT Analysis Set: All patients who receive at least 1 dose of study drug are assigned according to the treatment randomized.

- Microbiological ITT Analysis Set

  All patients in the ITT analysis set with an identified pretreatment pathogen.

- MITT Analysis Set All patients in the ITT analysis set who are hospitalized with a complicated skin and skin structure infection and met all study inclusion and exclusion criteria.

- Microbiological MITT Analysis Set

  All patients in the MITT analysis set with an identified pretreatment pathogen.

- CE Analysis Set All patients in the MITT analysis set who fulfill all predefined evaluability criteria.

- FE Analysis Set All patients in the CE analysis set with an identified pretreatment pathogen.

Patient Population

Of the 1076 Patients randomized to Study Drug:

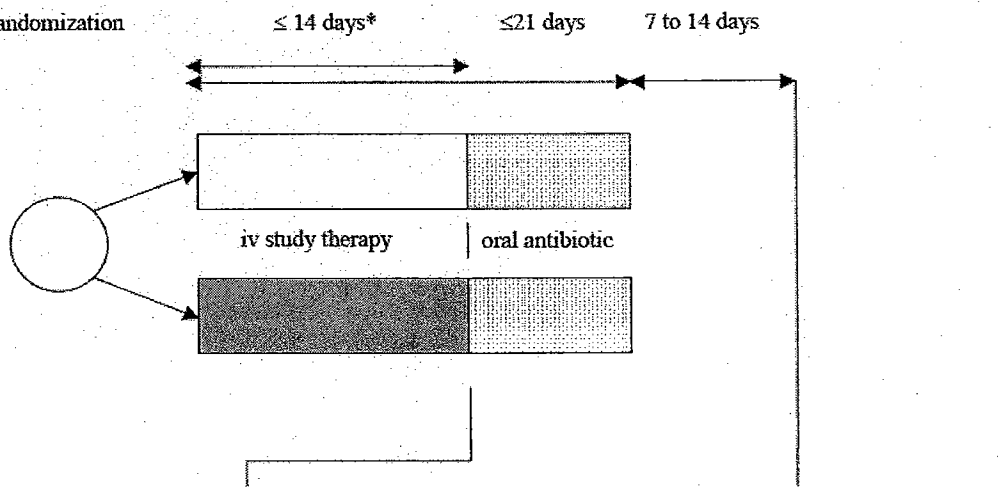
535 patients are randomized to receive meropenem;
541 are randomized to receive imipenem-cilastatin; and
39 patients did not receive study drug.

B. Study Plan and Procedures

Overall Study Design and Flow Chart

Figure 1* shows the overall design of the study.

Figure 1 Study design



* Patients received iv study therapy for at least 3 days while hospitalized. Patients who required more than 14 days of iv study therapy were determined to have unsatisfactory clinical outcomes.

Patients randomized to receive imipenem-cilastatin 500 mg iv every 8 hours

Patients randomized to receive meropenem 500 mg iv every 8 hours

Patients received oral antibiotic therapy (optional)

* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 5.1. Overall Study Design and Flow Chart, Figure 1, Page 30, Dated: 07/28/04.

Study Plan

Table 2* is a summary of the study procedures and assessments conducted at each time point.

	Pretreatment visit[a]	Treatment visit[b]	End-of-treatment visit[c]	Post-treatment follow-up visit[d]
General events/assessments				
Informed consent	X			
Inclusion/exclusion criteria	X			
Demographic data, medical history	X			
Surgical intervention/history[e]	X			
Pregnancy test[f]	X			
Prior medications[g]	X			
Pathogen testing[h]	X			
Primary infection diagnosis	X			
Physical examination including highest daily temperature	X			
Drug dispensing	X	X		
Efficacy assessments				
Signs and symptoms of infected area[i]	X	X	X	X
Wound site culture[j]	X	X[k]	X	X
Blood culture	X	X[l]	X[l]	X[l]
Concurrent therapy including adjunctive treatment for infection		X	X	X
Clinical response assessment			X	X[m]
Microbiological response assessment			X	X
Health care resource utilization[n]				X
Safety assessments				
Adverse events		X[o]	X	X
Clinical laboratory tests[p,q]	X	X	X	X

* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 5.1. Overall Study Design and Flow Chart, Table 1, Page 31, Dated: 07/28/04.

[a] The pretreatment visit was within 24 hours of entering the study unless otherwise specified.
[b] Assessments were made on days of iv study drug administration (no more than 14 days).
[c] The end-of-treatment visit occurred within 24 hours after the last administration of iv study drug.
[d] The post-treatment follow-up visit occurred from 7 days to 14 days after the last administration of antibiotic therapy for patients who did not experience a clinical response of failure at the end-of-treatment visit. If necessary, post-treatment follow-up visits were allowed to be conducted up to 28 days after the last administration of antibiotic therapy.
[e] Initial surgical interventions, if any, were for skin and skin structure infection.
[f] Serum or urine pregnancy tests were performed for women of child-bearing potential.

Table 2 (con't)

Summary of the Study Procedures and Assessments conducted at Each Time Point

[g] The use of medications, including antibiotics, administered within 14 days before the first infusion of study drug was recorded.

[h] All pathogens were to be susceptible to meropenem, imipenem, and any potential follow-up oral antibiotic according to agar disk diffusion or minimal inhibitory concentration dilution testing.

[i] Signs and symptoms of the infected area were highest daily body temperature, tachycardia, hypotension, impaired physical activity, limited oral intake, rigors, and, at the primary site, skin lesion erythema, skin lesion edema, induration, local heat, skin lesion pain, skin lesion tenderness, pustules, vesicles, bullae, desquamation, necrosis, fluctuation, skin lesion exudates, skin wound drainage, lymphangitis, and pruritus

[j] Wound site culture specimens were obtained by leading edge aspiration or by biopsy, needle aspiration, surgery, or deep swabs.

[k] As clinically indicated.

[l] Two blood cultures were taken, each from different sites or, if taken from a single site, separated by at least 30 minutes. If either blood culture was positive for a potential pathogen, 2 blood cultures were collected every 48 hours until the culture results were negative.

[m] Patients with a clinical response assessment of failure at the end-of-treatment visit did not require a response assessment at the post-treatment follow-up visit.

[n] Health care resource utilization data collected during the study were total length of hospital stay, number of infusions of study drug, number of days receiving infusion therapy, duration of oral antibiotic therapy, number of intensive care unit bed days, and number of days missed from work, school, and other activities since last infusion of study drug.

[o] Adverse events were recorded daily.

[p] The following laboratory tests were in the panel: hemoglobin, hematocrit, white blood cell count and differential, platelet count, creatinine, alanine aminotransferase, aspartate aminotransferase, and, if persistent diarrhea occurred, a stool sample was obtained to determine the presence of *Clostridium difficile* toxin. Additionally, in the event oral vancomycin was administered, the presence of this toxin was evaluated before initiation and at the discontinuation of vancomycin therapy.

[q] Laboratory tests to evaluate hematologic status and hepatic and renal function of patients were obtained within the 24-hour period prior to study treatment initiation, and were repeated during treatment as needed, at the end-of-treatment, and at the follow-up visit, if warranted. If therapy is longer than 1 week, laboratory tests were completed at least weekly.

C. Clinical Microbiology

Identification of Pathogens

Pathogens are identified to the genus and species level from specimens obtained by leading edge aspiration or deep cultures from each patient at the most extensive site of skin and skin structure infection. These specimens are obtained within 72 hours before administration of IV study drug. In specimens containing many aerobic and anaerobic bacteria (e.g., perirectal abscess), only those bacteria in predominance are required to be identified.

Susceptibility of Pathogens

Pathogens are tested for susceptibility to meropenem, imipenem, and any potential follow-up oral antibiotic. In specimens containing many aerobic and anaerobic bacteria (e.g., perirectal abscess), only those bacteria in predominance are required to be tested for susceptibility.

Organisms Expected in this Trial

- Cellulitis

S. pyogenes, other *β-hemolytic Streptococci*, *Staphylococcus aureus*, *Enterococcus* species, *Serratia* species, *Proteus* species, *Pseudomonas aeruginosa*, and other Enterobacteriaceae.

- Complex abscess, perirectal abscess, wound infections, infected ischemic/diabetic ulcers, and infections requiring significant surgical intervention:

S. aureus, *S. pyogenes*, other *β-hemolytic Streptococc*, Milleri streptococcus group (*S. anginosus*, *S. constellatus*, *S. intermedius*), microaerobic streptococci, *Enterococcus* species, *Proteus* species, *Morganella morganii*, *Providencia* species, other Enterobacteriaceae, *Escherichia coli*, *Pseudomonas* species, *Bacteroides fragilis* group, *Bacteroides species*, *Prevetella and Porphyromonas* species, *Fusobacterium* species, *Clostridium perfringens*, *Clostridium* species, *Peptostreptococcus* species, non-spore-forming anaerobic gram-positive bacilli.

Methods of Assessment

Susceptibility of rapidly growing aerobic and fastidious organisms to meropenem, imipenem, and any likely oral follow-up antimicrobial agent(s) is determined at each study center or other approved testing facility using MIC methodology (NCCLS-recommended method or an FDA-approved antimicrobial susceptibility device that can test both meropenem and imipenem) or the NCCLS agar disk diffusion method of Kirby-Bauer.

Susceptibility of anaerobic organisms to meropenem, imipenem, and any likely oral follow-up antimicrobial agent(s) is determined at each study center by _____, or submitted to _____ and tested by the dilution MIC method in Brucella agar according to NCCLS.

Methicillin (oxacillin) resistance in *Staphylococcus* species is required to be determined by oxacillin using the latest NCCLS guidelines (documents M7-A5 and M2-A7).

Clinical Microbiology Reviewer's Comments:

The Applicant is reminded that the [redacted] is not recognized for MIC susceptibility testing by the FDA and CLSI/NCCLS*.

* The Clinical and Laboratory Standards Institute (CLSI) is the new name for the former National Committee for Clinical Laboratory Standards (NCCLS) organization.

b. Calculation or Derivation of Outcome Variable

Meropenem and imipenem susceptibility disk zone sizes and MIC determinations are interpreted according to the NCCLS criteria in Table 3.

Table 3* shows the NCCLS zone diameter interpretive standards and minimum inhibitory concentration (MIC) breakpoints.

Antibacterial activity	Aerobes and anaerobes[a] (MIC breakpoints)	Aerobes[b] (zone diameter breakpoints)	*Streptococcus* species other than *S. pneumoniae*[a]
Meropenem (S)	≤4	≥16	≤0.5[c]
Meropenem (I)	8	14 to 15	See note d
Meropenem (R)	≥16	≤13	See note d
Imipenem (S)	≤4	≥16	See note e
Imipenem (I)	8	14 to 15	—
Imipenem (R)	≥16	≤13	—

* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 5.5.2.4. Susceptibility of Pathogens, (b) Calculation or Deviation of Outcome Variable, Table 5, Page 46, Dated: 07/28/04.

[a] Susceptibility determined by minimal inhibitory concentration methods, µg/mL.
[b] Susceptibility determined by disk diffusion methods, mm.
[c] Susceptibility can be based on penicillin susceptibility.
[d] The current absence of resistant strains precluded defining any categories other than susceptible.
[e] NCCLS does not currently assign an imipenem MIC value, but susceptibility can be based on penicillin susceptibility.
I Intermediate susceptibility, MIC Minimal inhibitory concentration, R Resistant, S Susceptible

Streptococci, other than *Streptococcus pneumoniae*, have an NCCLS-approved MIC breakpoint for meropenem only, but are considered susceptible to imipenem if susceptible to penicillin. ß-hemolytic streptococci are universally susceptible to penicillin and, therefore, to both meropenem and imipenem. Quality control of all susceptibility methods are practiced at each study center.

Methicillin (oxacillin)-resistant *Staphylococcus aureus* and coagulase-negative *Staphylococcus* species are assumed resistant to ß-lactams, including imipenem and meropenem, regardless of *in vitro* testing results to those antibiotics.

An organism isolated from the skin and skin structure cultures are also classified by its etiologic importance as defined in Table 4. These cultures can reveal other microorganisms that are colonizers, contaminants, or normal flora due to the collection method or culture processing.

Table 4* defines the study classifications of organisms.

Class	Definition
Pathogen	A bacterium that produced signs and symptoms of active infection
Colonizer	Microorganism or potential pathogen not considered normal flora recovered from the infection site in the absence of signs and symptoms of active infection
Normal flora	Indigenous microorganism associated with a particular body site
Contaminant	Foreign microorganism accidentally present

* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 5.5.2.4. Susceptibility of Pathogens, (b) Calculation or deviation of Outcome Variable, Table 6, Page 47, Dated: 07/28/04.

Table 5 defines the efficacy objective and related outcome variables.

Objective	Summary outcome variable for analysis (including timepoint and analysis sets)
• to demonstrate the therapeutic noninferiority of meropenem (500 mg iv every 8 hours) to imipenem-cilastatin (500 mg iv every 8 hours) in hospitalized patients with complicated skin and skin structure infections	Primary endpoints • clinical outcome at the post-treatment follow-up visit in the CE and MITT analysis sets (co-primary) Secondary endpoints • clinical outcome at the post-treatment follow-up visit in the ITT, microbiological ITT, microbiological MITT, and FE analysis sets • clinical outcome at the end-of-treatment visit in the CE, MITT, ITT, microbiological ITT, microbiological MITT, and FE analysis sets • clinical response at the end-of-treatment and post-treatment follow-up visits in the FE analysis set by pathogen • microbiological outcome at the end-of-treatment and post-treatment follow-up visits in the FE, microbiological ITT, and microbiological MITT analysis sets • pretreatment pathogen outcome at the end-of-treatment and post-treatment follow-up visits in the FE analysis set

Table 5* (con't) Efficacy Objective and Related Outcome Variables

Objective	Summary outcome variable for analysis (including timepoint and analysis sets)
	Additional measures • clinical outcome at the post-treatment follow-up visit in the CE analysis set by primary infection diagnosis • clinical outcome at the post-treatment follow-up visit in the CE analysis set by age, gender, race, and location of study center • clinical outcome at the post-treatment follow-up visit in the CE analysis set by diabetes mellitus • clinical outcome at the post-treatment follow-up visit in the CE analysis set by initial surgical intervention • concordance between clinical and microbiological outcomes at the post-treatment follow-up visit in the CE analysis set • time to hospital discharge

* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 5.5.3.1. Summary of Efficacy Variable of the Study to the Study Objective, Table 7, Pages 48 & 49, Dated: 07/28/04.

Primary Variable: Clinical Outcome at Post-Treatment Follow-up Visit.

(a) Methods of assessment

Clinical outcome at the post-treatment follow-up visit is a function of the clinical response assessed by evaluating the following signs and symptoms of the primary skin and skin structure infection: highest daily body temperature, tachycardia, hypotension, impaired physical activity, limited oral intake, rigors, and, at the primary site, skin lesion erythema, skin lesion edema, induration, local heat, skin lesion pain, skin lesion tenderness, pustules, vesicles, bullae, desquamation, necrosis, fluctuation, skin lesion exudates, skin wound drainage, lymphangitis, and pruritus. The extent of infection is measured by the maximum width and length of the infected site.

(b) Calculation or derivation of outcome variable

Clinical outcome at the post-treatment follow-up visit has values of satisfactory or unsatisfactory depending upon the clinical response assessment as shown in Table 6:

Table 6* shows the relationship between investigator-assessed clinical response and clinical outcome at the primary endpoint.

Visit	Investigator-assessed clinical response	Clinical outcome
Post-treatment follow-up	Cure	Satisfactory
	Failure	Unsatisfactory
	Relapse	Unsatisfactory

*Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 5.5.3.2. Primary Variable: Clinical Outcome at Post-treatment follow-up Visit, Table 8, Page 50, Dated: 07/28/04.

Clinical response is determined by the investigator to be either cure, failure, or relapse according to the following definitions:

Cure: All signs and symptoms of the skin and skin structure infection adequately resolve or improve to such an extent that no further antibacterial therapy is necessary

Failure: Clinical signs and symptoms of the skin and skin structure infection worsen or are not adequately improved. Patients who require more than 14 days of iv study drug or more than 21 days of IV study drug and oral antibiotic therapy are considered to have had clinical responses of failure.

Relapse: signs and symptoms of the skin and skin structure infection considered cured or improved at end of treatment, but returned at the post-treatment follow-up visit

Secondary Variable: Microbiological outcome.

Microbiological outcome is a function of the microbiological response assessed by evaluating the relationship between the pretreatment pathogens at the end-of-treatment and post-treatment follow-up visits. Microbiological response is assessed only in those patients who had a positive pretreatment culture of the primary infection site, or a pretreatment blood culture with at least 1 organism classified as a pathogen.

All bacterial pathogens are considered in determining the microbiological outcome, i.e., pathogens identified before treatment and new pathogens identified after treatment.

NOTE: Diphtheroids, Corynebacterium, and "normal" flora classified by the investigator as pathogens before treatment are not counted as pretreatment pathogens.

(a) Methods of assessment

A specimen from the most extensive site of skin and skin structure infection is obtained by leading edge aspiration from patients with cellulitis. Pathogens in specimens collected by leading edge aspiration are cultured to identify aerobic pathogens at each study center or other approved testing facility according to institutional methods and tested for susceptibility according to NCCLS-approved techniques [NCCLS: M7-A5 (2000a) and M2-A7 (2000b)].

A deep specimen (such as from biopsy, needle aspiration, surgically obtained specimens, or deep swabs of fluids/pus) from the most extensive site of skin and skin structure infection is obtained from patients with any of the following infections: complex abscess, perirectal abscess, wound infections, infected ischemic/diabetic ulcers, and infections requiring significant surgical intervention. Pathogens in specimens collected by these techniques are cultured to identify anaerobic, aerobic, mycobacterial, and fungal pathogens by local laboratories and/or Covance (Indianapolis, IN) according to institutional methods and tested for susceptibility according to NCCLS-approved techniques [NCCLS: M7-A5 (2000a) and M2-A7 (2000b)].

Additionally, from all patients, blood is collected either from 2 sites concurrently, or from a single site at 2 times separated by 30 minutes. If blood cultures are positive for any pathogen, blood is collected every 48 hours until there is no growth.

Table 7* shows the relationship between Applicant-assessed microbiological response and microbiological outcome by treatment visit.

Visit	Sponsor-assessed microbiological response	Microbiological outcome
Post-treatment follow-up	Documented eradication	Satisfactory
	Presumed eradication	Satisfactory
	Colonization	Satisfactory
	Presumed persistence	Unsatisfactory
	Recurrence	Unsatisfactory
	Reinfection	Unsatisfactory
	Missing data	Unsatisfactory

* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 5.5.3.4. Secondary Variable: Microbiological Outcome, (b) Calculation or Deviation of Outcome Variable, Table 10, Page 52, Dated: 07/28/04.

Microbiological response is determined by the Applicant based upon the precedence of culture sites according to the algorithm below. If a positive culture is obtained from both primary site and a blood culture, both results are used to determine the overall microbiological response. A primary site response of no growth takes precedence unless the blood culture was positive. If the primary site has no material to culture or is not assessed, then a positive blood culture takes precedence; the primary site result took precedence if the blood culture is negative or not done.

Post-treatment Follow-up visit

Microbiological responses of documented persistence, presumed persistence, and superinfection at the end-of-treatment visit are carried forward to the post-treatment follow-up visit.

If there is no material to culture ["not cultured" box checked on Case Report Form (CRF)] and the microbiological response at the end-of-treatment visit is documented eradication, presumed eradication, colonization, or missing data, then the microbiological response is dependent upon the clinical response:

> If the clinical response is cure, then the microbiological response is presumed eradication;
>
> If the clinical response is failure or relapse, then the microbiological response is presumed persistence; and
>
> If the clinical response is missing, then the microbiological response is recurrence.

If the culture result is "no growth" and the microbiological response at the end-of-treatment visit is documented eradication, presumed eradication, colonization, or missing data, then the microbiological response is documented eradication.

If the culture result is "growth" and the microbiological response at the end-of-treatment visit is documented eradication, presumed eradication, colonization, or missing data:

If the only organisms isolated are diphtheroids, Corynebacterium, or "normal" flora, then the microbiological response is documented eradication

If any of the pretreatment pathogens are present, then the microbiological response is recurrence

If the organisms are not in the pretreatment culture and are not diphtheroids, Corynebacterium, or "normal" flora, then the microbiological response is determined by the clinical outcome:

If the clinical outcome is satisfactory, then the microbiological response is colonization

If the clinical outcome is unsatisfactory, then the microbiological response is reinfection

If there is no microbiological response assessment (line slashed through CRF page) and the microbiological response at the end-of-treatment visit is documented eradication, presumed eradication, colonization, or missing data, then the microbiological response is missing data.

Laboratory Safety Measurements and Variables

Table 8* shows the assessment of the laboratory safety variables.

Type of assessment	Variables
Hematology	Hemoglobin, hematocrit, white blood cell count and differential, and platelet count
Clinical chemistry	
Hepatic function	Alanine aminotransferase and aspartate aminotransferase
Renal function	Creatinine
Other	*Clostridium difficile* in a stool specimen in the event of persistent diarrhea

* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 5.5.5.3 Laboratory Safety Measurements and Variables, al Outcome, (b) Calculation or Deviation of Outcome Variable,, Table 13, Page 60, Dated: 07/28/04.

Laboratory specimens are collected and analyzed by local laboratories.

Any clinically significant abnormal laboratory value(s) is to be followed until it returned to normal or become stabilized. The investigator is to record any clinically significant adverse laboratory changes on the adverse events page of the CRF and give an opinion as to their causality.

Description of Analysis Sets

Table 9* shows the relationships between the analysis sets.

Analysis set	Contained within	Partial description[a]	Purpose
Safety	—	Received at least 1 administration of iv study drug Assigned by treatment received	To assess safety
ITT	—	Received at least 1 administration of iv study drug Assigned by treatment randomized	Supportive analysis
MITT	ITT	Met all inclusion and exclusion criteria Hospitalized with a complicated skin and skin structure infection	To assess primary endpoint
CE[b]	MITT	A specimen for culture and susceptibility testing was obtained within 72 hours of starting study drug therapy Study drug was administered as randomized without modification for a minimum of 72 hours, unless the patient was a clinical failure at 48 hours Two doses of study drug were not missed during the first 48 hours of treatment, or 2 consecutive doses were not missed at anytime during treatment Prior antibiotic therapy was not administered for more than 24 hours within 14 days of starting study drug therapy, unless a pretreatment culture obtained within 72 hours before starting study drug therapy showed persistence of a pathogen in blood or at the site of infection No other systemic antibacterials active against the pathogen associated with the skin and skin structure infection were coadministered with the study drug for treatment of the skin and skin structure infection. No antibiotic therapy was given after the entry culture was obtained and prior to the initiation of study therapy. Patients requiring more than 14 days of iv antibiotic therapy at the end-of-treatment or post-treatment follow-up visits or more than 21 days of combined iv and oral antibiotic therapy at the post-treatment follow-up visit were considered treatment failures.	To assess primary endpoint

Table 9* (con't) Relationships between Analysis Sets

Analysis set	Contained within	Partial description[a]	Purpose
Microbiological ITT	ITT	Pathogen identified in the baseline culture	Supportive analysis
Microbiological MITT	MITT	Pathogen identified in the baseline culture	Supportive analysis
FE	CE	A pathogen considered to be the cause of the complicated skin and skin structure infection was isolated from the pretreatment culture All pathogens isolated at study entry were susceptible to both study drugs	Supportive analysis

* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 5.7.3 Description of Analysis Sets, Table 14, Pages 60 to 63, Dated: 07/28/04.

[a] Significant, but partial, descriptions of analysis sets are listed. Complete criteria are presented in text.
[b] Patients were in the clinically evaluable analysis set irrespective of whether pathogens were isolated from the pretreatment specimen.
CE Clinically evaluable, FE Fully evaluable, ITT Intention-to-treat, MITT Modified intention-to-treat

Clinical Microbiology Reviewer's comment:

NOTE: The FDA significant population analysis set is the "fully evaluable (FE)" and its associated "microbiological outcome" results.

Clinically Evaluable Analysis Set

Patients in the CE analysis set are also in the MITT analysis set. Patients who met all the following criteria are in the CE analysis set:

1. Patients meet all inclusion and exclusion criteria.

2. Patients meet the definition of complicated skin and skin structure infection in the modified intention-to–treat (MITT) analysis set and an adequate description of the infected area is provided.

3. Within 72 hours before the initiation of study treatment, a specimen from the infected area is obtained for culture and susceptibility testing. Patients with no pathogen isolated are considered clinically evaluable only.

4. Signs and symptoms of infection (including highest daily temperature) are assessed and recorded at entry, daily during therapy, at the end-of-treatment visit, and at the post-treatment follow-up visit.

5. Original randomized study drug regimen is administered without modification for a minimum of 72 hours, unless the patient is a clinical failure at 48 hours.

6. Two doses of study drug are not missed during the first 48 hours of treatment, or 2 consecutive doses are not missed at anytime during treatment.

7. Prior antibiotic therapy is not administered for more than 24 hours within 14 days of study treatment initiation unless a pretreatment culture obtained within 72 hours of the initiation of study therapy showed persistence of a pathogen in blood or at the site of infection. Patients who receive no more than 24 hours of antibiotic therapy before study entry are considered clinically evaluable if the culture obtained at study entry reveals no growth.

8. No other systemic antibacterials active against the pathogen associated with the skin and skin structure infection are co-administered with the study drug for treatment of the skin and skin structure infection; if they are, the patient is considered an evaluable treatment failure (if study drug was administered for more than 48 hours). If the systemic antibacterials are given for treatment of another infection, the patient is considered non-evaluable. No antibiotic therapy is allowed after the entry culture is obtained and before initiation of study therapy.

9. A post-treatment follow-up evaluation is performed from 7 to 14 days (although up to 28 days is allowed) after study treatment ended or after the oral antibacterial agent has been discontinued for patients who transitioned to oral antibiotics. Patients requiring more than 14 days of IV antibiotic therapy are considered treatment failures at the end-of-treatment and post-treatment follow-up visits, and patients requiring more than 21 days of combined IV and oral antibiotic therapy are considered treatment failures at the post-treatment follow-up visit. Additionally, patients without documented post-treatment follow-up visits who have unsatisfactory clinical outcomes at the end-of-treatment visits are classified as evaluable treatment failures at the
end-of-treatment and post-treatment follow-up visits. A clinical failure at the end-of-treatment visit did not require a post-treatment follow-up evaluation.

10. All CRFs are completed appropriately.

Microbiology Changes in the Conduct of the Study

Key microbiology amendments to the study protocol are shown in table 10, as follows:

Table 10 **Microbiology Protocol Amendments**

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Persons who initiated amendment[a]
7 Jul 2001	A patient was considered clinically evaluable if, within 72 hours before initiation of study drug therapy, a specimen for culture and susceptibility test was obtained from the infected site.	Update Timing for pretreatment culture	Clinical Study Team
7 Jul 2001	All antibiotic therapies were disallowed after the entry culture was obtained and before study therapy was initiated.	Update concomitant medications	Clinical Study Team
7 Jul 2001	Previously, patients who did not receive a post-treatment follow-up assessment within 28 days of the end-of-treatment visit were considered nonevaluable.	Update evaluability criteria	Clinical Study Team
7 Jul 2001	Patients requiring more than 14 days of therapy with intravenous study drugs or more than 21 days of therapy with intravenous study drugs and oral antibiotics were considered treatment failures.	Update allowable maximum duration of iv and/or oral therapy as per negotiation with the FDA	Clinical Study Team
7 Jul 2001	Previously, patients who did not receive a post-treatment follow-up assessment within 28 days of the end-of-treatment visit were considered nonevaluable.	Update evaluability criteria	Clinical Study Team

Table 10* (con't) Microbiology Protocol Amendments

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Persons who initiated amendment[a]
7 Jul 2001	To be considered clinically and fully evaluable, 2 doses of study drug were not to be missed and no antibiotic therapy was permitted after obtaining the entry culture and before initiation of study drug therapy. Previously, no more than 2 doses of study drug were to be missed and the restriction on antibiotic therapy was not stated.	Update Evaluability criteria	Clinical Study Team
12 Jun 2002	The number of participating centers was increased to 100 domestic and international centers from 45 to 60 medical centers.	To increase patient enrollment	Clinical Study Team
12 Jun 2002	Patients were allowed to enter the study if they received more than 24 hours of antibacterial therapy within 14 days of study entry if a persistent pathogen was found in blood or at the infection site; if the entry culture result was "no growth", patients were nonevaluable. Patients who received no more than 24 hours of antecedent antibacterial therapy were allowed to enter if the entry culture result was "no growth".	Update requirement of a positive culture	Clinical Study Team

Table 10* (con't) Microbiology Protocol Amendments

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Persons who initiated amendment[a]
12 Jun 2002	The number of patients enrolled was increased from 630 to 790 in order to obtain 504 clinically evaluable patients.	Increase the Sample size because of the potential to compromise the blind of patients with dose reductions attributed to renal function	Clinical Study Team
25 Feb 2003	The number of patients enrolled was increased to approximately 1000 in order to obtain 402 clinically evaluable patients. Previously, 790 patients were to be enrolled to obtain 504 clinically evaluable patients. The number of patients required to maintain 80% power was reduced from 252 patients per treatment group to 201.	To increase statistical power	Clinical Study Team

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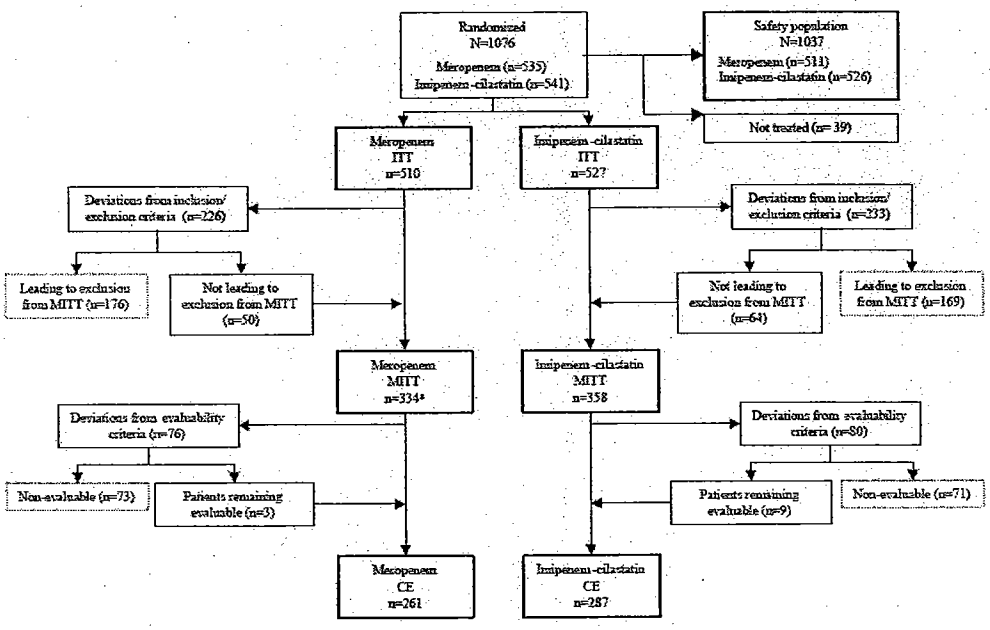
* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 5.8.1, Changes in the Conduct of the Study, Table 16, Protocol Amendment, A. Clinical Analysis Sets, Pages 72 to 75, Dated: 07/28/04.

[a] All protocol amendments are approved within AstraZeneca and at study centers before being implanted.

Patient Populations Analyzed (analysis sets)

The analysis sets and the number of patients in the clinical and microbiology analysis set are summarized, in Figures 2A and 2B, s follows:

Figure 2A* **Clinical Patient Population Analysis Sets**



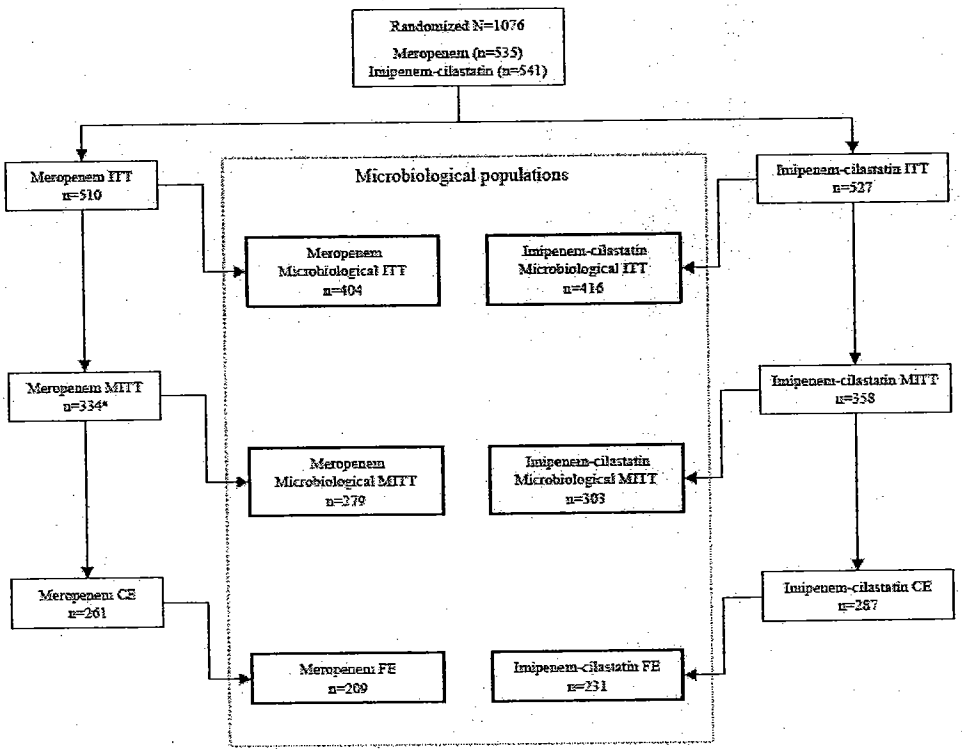
* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 6.4 Patient Populations Analyzed (analysis sets), Figure 3, Analysis Sets, A. Clinical Analysis Sets, Page 88, Dated: 07/28/04.

[a] Four patients (Patients 0001/00105, 0054/05408, 0057/05708, and 0105/10519), each randomized to meropenem, had a deviation that should have led to their exclusion from the modified intention-to-treat analysis set, but they are erroneously included in this analysis set.

CE = clinically evaluable; FE = fully evaluable; ITT = intention-to-treat; MITT = modified intention-to-treat.

Figure 2B*

Microbiological Patient Population Analysis Sets



* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 6.4 Patient Populations Analyzed (analysis sets), Figure 3, Analysis Sets, A. Microbiological Analysis Sets, Page 89, Dated: 07/28/04.

[a] Four patients (Patients 0001/00105, 0054/05408, 0057/05708, and 0105/10519), each randomized to meropenem, had a deviation that should have led to their exclusion from the modified intention-to-treat analysis set, but they were erroneously included in this analysis set.

CE = clinically evaluable; FE = fully evaluable; ITT = intention-to-treat; MITT = modified intention-to-treat.

Pathogen Susceptibility

Among the pretreatment pathogens isolated from patients in the microbiological ITT analysis set, there are no clinically relevant differences in *in vitro* susceptibility to meropenem and imipenem-cilastatin. The most common pathogens isolated at least 50 times are:

Gram-positive aerobes:	*Staphylococcus aureus* (total), methicillin susceptible, and methicillin resistant; Viridans Streptococcus species (total); *Streptococcus pyogenes* (Group A); *Streptococcus agalactiae* (Group B); Streptococcus species, other (total); and *Enterococcus faecalis*
Gram-negative aerobes:	*Escherichia coli* (total), Proteus species (total), and *Pseudomonas aeruginosa*
Gram-positive anaerobes:	Peptostreptococcus species (total)
Gram-negative anaerobes:	*Bacteroides fragilis* group (total)

Microbiological Outcome

Secondary efficacy analyses of satisfactory microbiological outcomes and the difference in satisfactory outcomes between treatment groups at the end-of-treatment and post-treatment follow-up visits are summarized in Table 11 and Table 12, respectively. The differences in the proportions of patients with successful microbiological outcomes in these secondary analyses support the results of the primary analysis.

Table 11* shows the secondary efficacy analyses of satisfactory microbiological outcomes at the post-treatment follow-up visit (by analysis set by subgroup)

Analysis set Subgroup	Meropenem			Imipenem-cilastatin			Difference[a] (95% CI)
	N	n	%	N	n	%	
FE							
All patients	209	166	79.4	231	183	79.2	0.2 (–7.4, 7.8)
No dose adjustment[b]	194	155	79.9	207	167	80.7	–0.8 (–8.6, 7.0)
With dose adjustment[c]	15	11	73.3	24	16	66.7	6.7 (–22.6, 35.9)
Microbiological MITT							
All patients	279	182	65.2	303	207	68.3	–3.1 (–10.7, 4.6)
No dose adjustment[b]	256	167	65.2	269	188	69.9	–4.7 (–12.7, 3.4)
With dose adjustment[c]	23	15	65.2	34	19	55.9	9.3 (–16.3, 35.0)
Microbiological ITT							
All patients	404	209	51.7	416	236	56.7	–5.0 (–11.8, 1.8)
No dose adjustment[b]	371	194	52.3	361	210	58.2	–5.9 (–13.1, 1.3)
With dose adjustment[c]	33	15	45.5	55	26	47.3	–1.8 (–23.3, 19.7)

* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 7.2.2.2 Microbiological Outcome Table 38, Page 111, Dated: 07/28/04.

[a] Meropenem minus imipenem-cilastatin with 95% confidence interval. This study is not powered to detect statistically significant differences for any of the analyses presented in this table; adjustments are not made for multiple comparisons.

[b] The study blind is preserved in this subgroup of patients who did not require a dosage reduction because of renal function.

[c] The study blind may have been compromised in some patients in this subgroup of patients who did require a dosage reduction because of renal function.

CI = Confidence interval., FE = Fully evaluable, ITT = Intention-to-treat, and MITT = Modified intention-to-treat.

Clinical Microbiology Reviewer's Comments:

In the aforementioned Table 11, in the "fully evaluable (FE)" population, the percentage of satisfactory microbiological outcomes at the post-treatment follow-up visit is higher in all "Analysis Set Subgroups" than the comparator drug [Primaxin I.V. (Imipenem-cilastatin)].

Clinical and Microbiological Outcome Concordance

Concordance between clinical outcome and microbiological outcome is summarized for the FE analysis set in the below Table 12. The proportion of patients in the FE analysis set with concordant clinical and microbiological outcomes is similar in each treatment arm, at each visit. In general, the proportion of patients with concordant satisfactory microbiological and clinical outcomes was at least 90% for both treatment groups at both assessments. The proportion of patients with concordant unsatisfactory microbiological and clinical outcomes is at least 80.0% at the end-of-treatment visit and 100.0% at the post-treatment follow-up visit. There are no clinically relevant differences in concordance between treatment groups or between times of assessment.

Table 12[1] shows the concordance between clinical and microbiological response (FE analysis set)

Microbiological outcome	Clinical outcome							
	Meropenem N=209				Imipenem-cilastatin N=231			
	Satisfactory		Unsatisfactory		Satisfactory		Unsatisfactory	
	n	%[2]	n	%[2]	n	%[2]	n	%[2]
End-of-treatment visit								
Satisfactory	180	90.9	2	18.2	206	95.4	3	20.0
Unsatisfactory	18	9.1	9	81.8	10	4.6	12	80.0
Post-treatment follow-up visit								
Satisfactory	166	89.7	0		183	95.3	0	
Unsatisfactory	19	10.3	24	100.0	9	4.7	39	100.0

[1] Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 7.2.2.3 Clinical and Microbiological Outcome Concordance, Table 38, Page 112, Dated: 07/28/04.

Pretreatment Pathogen Outcome

The proportions of patients in the FE analysis set with satisfactory pretreatment pathogen outcomes by pathogen are compared with the proportions of patients with satisfactory clinical outcomes at the end-of-treatment and post-treatment follow-up visits in Table 13. Among the most common pretreatment pathogens isolated from at least 10 patients in the FE analysis set, there are no clinically relevant differences between treatment groups in the proportion of patients with clinically successful outcomes at either time of assessment. The most common pathogens isolated from at least 10 patients randomized to meropenem are:

Gram-negative aerobes:	*Escherichia coli*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*
Gram-negative anaerobes:	*Bacteroides fragilis*
Gram-positive aerobes:	*Staphylococcus aureus*, methicillin susceptible; *Streptococcus pyogenes* (Group A); *Streptococcus agalactiae* (Group B); *Streptococcus viridans* Group, nos; and *Enterococcus faecalis*

Clinical Microbiology Reviewer's comments:

As shown in the following Table 13, the proportions of satisfactory clinical outcomes for patients in the meropenem-treated group infected with any of these common pretreatment pathogens at the post-treatment follow-up visit ranged from 93.2% for 88 patients infected with methicillin susceptible *Staphylococcus aureus* to 70.6% for 17 patients infected with *Streptococcus agalactiae* (Group B). For 12 patients infected with *Enterococcus faecalis*, it is 75.0% and 84.6% for 13 patients infected with *Proteus mirabilis*. There are no clinically relevant differences between the proportion of patients with satisfactory pretreatment pathogen outcomes and corresponding proportions of patients with satisfactory clinical outcomes.

Table 13 Number (%) of patients with satisfactory pretreatment pathogen outcomes and number (%) of patients with satisfactory clinical outcomes for common pathogens found in at least 10 patients in either treatment group at the post-treatment follow-up visit (FE analysis set)

Pathogen class Pathogen[a]	Meropenem N=209					Imipenem-cilastatin N=231				
		Satisfactory pretreatment pathogen outcomes		Satisfactory clinical outcomes			Satisfactory pretreatment pathogen outcomes		Satisfactory clinical outcomes	
	N	n	%	n	%	N	n	%	n	%
Gram-positive aerobes										
Staphylococcus aureus, methicillin susceptible	88	69	78.4	82	93.2	100	83	83.0	84	84.0
Streptococcus pyogenes (Group A)	29	27	93.1	26	89.7	32	29	90.6	28	87.5
Streptococcus agalactiae (Group B)	17	14	82.4	12	70.6	19	16	84.2	16	84.2
Enterococcus faecalis	12	9	75.0	9	75.0	20	13	65.0	14	70.0
Streptococcus viridans Group, nos	12	11	91.7	11	91.7	6	5	83.3	5	83.3
Streptococcus milleri	5	4	80.0	4	80.0	11	11	100.0	11	100.0
Gram-negative aerobes										
Escherichia coli	15	12	80.0	12	80.0	21	14	66.7	15	71.4
Pseudomonas aeruginosa	15	10	66.7	11	73.3	15	14	93.3	13	86.7
Proteus mirabilis	13	11	84.6	11	84.6	7	5	71.4	6	85.7
Anaerobes										
Bacteroides fragilis	11	10	90.9	10	90.9	10	9	90.0	9	90.0

Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 7.2.2.4 Pretreatment Pathogen Outcome, Table 41, Pages 116 & 117, Dated: 07/28/04. [a] Patients may have more than one pretreatment pathogen. FE = Fully evaluable; nos = Not otherwise specified

Applicant's Conclusions on Efficacy Results

Table 14* summarizes some of the Applicant's efficacy objectives, variables, and conclusions.

Objective	Variable	Conclusion
To demonstrate the therapeutic noninferiority of meropenem (500 mg administered intravenously every 8 hours) and imipenem (500 mg administered intravenously every 8 hours) in hospitalized patients with complicated skin and skin structure infections	Clinical outcome at the post-treatment follow-up visit in the clinically evaluable and modified intention-to-treat analysis sets	This study demonstrated the noninferiority of meropenem (500 mg administered intravenously every 8 hours) to imipenem-cilastatin (500 mg administered intravenously every 8 hours) in the treatment of patients with clinical evidence of complicated skin and skin structure bacterial infection. There are no clinically relevant differences between treatment groups in the proportion of satisfactory outcomes based on primary infection diagnosis. There are no clinically relevant differences between treatment groups in the proportion of satisfactory outcomes for common pretreatment pathogens. There are no clinically relevant differences between treatment groups in the proportion of satisfactory outcomes for patients with initial surgical intervention. The proportion of patients in the FE analysis set with concordant clinical and microbiological outcomes was similar in each treatment arm, at each visit.

==========

* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 7.7 Conclusions of Efficacy Results, Table 43, Page 121, Dated: 07/28/04.

Discussion

Study Objectives

The purpose of the clinical study is to demonstrate the safety, tolerability, and efficacy of meropenem (500 mg I every 8 hours) as treatment for hospitalized patients with complicated skin and skin structure infections.

The primary objective is to demonstrate the therapeutic noninferiority of meropenem (500 mg iv every 8 hours) to imipenem-cilastatin (500 mg iv every 8 hours).

The secondary objective is to assess the safety and tolerability of meropenem (500 mg IV every 8 hours) administered in hospitalized patients with complicated skin and skin structure infections.

One thousand seventy-six patients are enrolled in this randomized, double-blind, comparative study. The enrolled population is broadly representative of the clinical patient population with complicated skin and skin structure infections.

Efficacy Results

The study is to demonstrate the noninferiority of meropenem (500 mg iv every 8 hours) to imipenem-cilastatin (500mg iv every 8 hours) for treatment of hospitalized patients with complicated skin and skin structure infections.

The following Table 15 shows a summary of key efficacy analysis.

Table 15 **Satisfactory Clinical Outcomes at the Post Treatment Follow-up Visit**

Analysis set	Meropenem			Imipenem			95% CI
	N	n	%	N	n	%	
CE	261	225	86.2	287	238*	82.9	–2.8, 9.3[a]
MITT	334	244	73.1	358	268	74.9	–8.4, 4.7[a]
ITT	510	295	57.8	527	325	61.7	–9.8, 2.1
FE	209	185	88.5	231	192	83.1	–1.1, 11.9
Microbiological MITT	279	205	73.5	303	225	74.3	–7.9, 6.4
Microbiological ITT	404	233	57.7	416	258	62.0	–11.1, 2.4

* Adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, 9.1.2 Efficacy Results, Table 67, Page 172, Dated: 07/28/04.

[a] Co-primary efficacy analysis.

CE = Clinically evaluable, CI = Confidence interval, FE = Fully evaluable, ITT = Intention-to-treat, and MITT = Modified intention-to-treat

Additional (secondary analyses) included the clinical outcomes of the ITT, microbiological ITT, microbiological MITT, and FE analysis sets at the post-treatment follow-up visit and the clinical outcome of all analysis sets at the end of treatment.

The analyses of the microbiological outcome at the end of treatment and follow-up visits in the microbiologically documented infections (FE, microbiological MITT, and microbiological ITT) are also supportive. Additionally, the results demonstrated that the clinical and microbiological outcomes were broadly concordant for both meropenem and imipenem-cilastatin.

Results of clinical and pretreatment pathogen outcomes support the efficacy of meropenem as treatment for complicated skin and skin structure infections caused by susceptible aerobic Gram-positive, aerobic Gram-negative, and anaerobic pathogens, including methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pyogenes* (Group A), *Streptococcus agalactiae* (Group B), *Enterococcus faecalis*, *Streptococcus viridans* Group, nos, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, [redacted] and *Bacteroides fragilis*.

Clinical Microbiology Summary Results for Clinical Study 3591L0079

The following is a summary of clinical response, microbiological response, and pretreatment pathogen response for all pretreatment pathogens. Clinical and microbiology outcomes for the proposed targeted pathogens and are shown in Table 16.

Table 16[*] Number and percentage of patients with satisfactory clinical, microbiological, and pretreatment pathogen outcomes for the proposed targeted organisms at the "post-treatment follow-up visit" (Fully Evaluable analysis set)

Pathogen Class / Pathogen[a]	Meropenem							Imipenem-cilastatin						
		Satisfactory Clinical Outcomes		Satisfactory microbiological outcomes		Satisfactory pretreatment pathogen outcomes			Satisfactory Clinical Outcomes		Satisfactory microbiological outcomes		Satisfactory pretreatment pathogen outcomes	
	N	n	%	n	%	n	%	N	n	%	n	%	n	%
Gram-positive aerobes														
Staphylococcus aureus, methicillin susceptible	88	82	93.2	68	77.3	69	78.4	100	84	84.0	80	80.0	83	83.0
Streptococcus pyogenes (Group A)	29	26	89.7	26	89.7	27	93.1	32	28	87.5	27	84.4	29	90.6
Streptococcus agalactiae (Group B)	17	12	70.6	10	58.8	14	82.4	19	16	84.2	14	73.7	16	84.2
Enterococcus faecalis	12	9	75.0	8	66.7	9	75.0	20	14	70.0	13	65.0	13	65.0
Streptococcus viridans Group, nos	12	11	91.7	11	91.7	11	91.7	6	5	83.3	5	83.3	5	83.3
Gram-negative aerobes														
Escherichia coli	15	12	80.0	12	80.0	12	80.0	21	15	71.4	13	61.9	14	66.7
Pseudomonas aeruginosa	15	11	73.3	10	66.7	10	66.7	15	13	86.7	13	86.7	14	93.3
Proteus mirabilis	13	11	84.6	9	69.2	11	84.6	7	6	85.7	4	57.1	5	71.4
Anaerobes														
Bacteroides fragilis	11	10	90.9	10	90.9	10	90.9	10	9	90.0	8	80.0	9	90.0
Peptostreptococcus species[c]	16	13	81.3	13	81.3	13	81.3	21	18	85.7	18	85.7	18	85.7

[*] Adapted from eNDA 50-706/SE1-018, eDocument 2671924, AstraZeneca, Study Code: 3591IL0079, Table 2, Dated: 02/16/05. Data adapted from eNDA 50-706/SEI-018, eDocument 2596336, AstraZeneca, Study Code: 3591IL0079, Table 11.2.4.1, Table 11.2.4.2, and Table 11.2.4.3, Pages 830 to 953, Dated: 07/28/04.

[a] Patients may have more than one pretreatment pathogen.

nos Not otherwise specified

1. The following is a summary of the microbiological eradication rates on the Fully Evaluable (FE) population for the aforementioned Table 16, Clinical Study 3591L0079:

   Staphylococcus aureus (methicillin susceptible) for meropenem is 78.4% (69/88 isolates) and for imipenem-cilastatin it is 83% (83/100 isolates);

   Enterococcus faecalis for meropenem is 75% (9/12 isolates) and for imipenem-cilastatin it is 65% (13 isolates).

   [redacted]

   Proteus mirabilis for meropenem is 84.6% (11/13 isolates) and for imipenem-cilastatin it is 71.4% (5/7 isolates).

   Peptostreptococcus species for meropenem is 81.3% (13/16 isolates) and for imipenem-cilastatin it is 85.7 (18/21 isolates). Microbiologically, for this particular bacterial labeling nomerclature, "*Peptostreptococcus* species" is permitted in the PI labeling.

   [redacted]

2. There is no data on meropenem activity against community-acquired or hospital-acquired methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* that harbor or express the Panton-Valentine leucocidin gene(s)."

IV. CONCLUSIONS

The Clinical Microbiology Reviewer recommends "approval" for NDA 50-706/SE1-018.

From the Clinical Microbiology Reviewer's perspective, the clinical microbiological data on NDA 50-706/SE1-018 for the treatment of complicated skin and skin structure infections (cSSSI) due to *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus pyogenes, Streptococcus agalactiae,* viridans group streptococci, *Enterococcus faecalis* (excluding vancomvcin-resistant isolates), *Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Bacteroides fragilis* and *Peptostreptococcus* species are satisfactory.

WITHHOLD 18 PAGE(S)

Draft Labeling

Microbiology Review

Harold V. Silver
Clinical Microbiology Reviewer
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APPROVAL

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/s/

Harold Silver
5/26/05 11:03:49 AM
MICROBIOLOGIST

Please sign off on the Clinical Microbiology Review, sNDA 50-706/SE1-018, MERREM (meropenem) IV for the treatment of cSSSI.

Frederic Marsik
5/26/05 11:24:51 AM
MICROBIOLOGIST

Lillian Gavrilovich
6/1/05 04:13:26 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-706 / S-018

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA#	50-706 (SE1-018)
PRODUCT	Meropenem for injection (Merrem® IV)
FORMULATION	Sterile powder, 500 mg and 1000 mg vials
SUBMISSION DATE	July 28, 2004
SUBMISSION TYPE	NDA Efficacy Supplement
SPONSOR	AstraZeneca Pharmaceuticals LP, Wilmington, DE 19803-8355
OCPB DIVISION	Division of Pharmaceutical Evaluation III
MEDICAL DIVISION	Division of Anti-Infective Drug Products
REVIEWER	Charles R. Bonapace, Pharm.D.
TEAM LEADER	Venkat R. Jarugula, Ph.D.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

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1. EXECUTIVE SUMMARY

AstraZeneca Pharmaceuticals LP submitted a New Drug Application (NDA) efficacy supplement to gain approval of meropenem for injection (500 mg q8h) as single agent therapy for the treatment of complicated skin and skin structure infections (cSSSIs) due to *Staphylococcus aureus* (methicillin-susceptible strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Enterococcus faecalis*, Viridans group streptococci, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, ——— Peptostreptococcus species, ———, and *Bacteroides fragilis*. The sponsor performed a single Phase 3 randomized, multicenter, double-blind, comparative clinical study to compare the clinical efficacy and safety of meropenem and imipenem in the treatment of hospitalized patients with cSSSI. In addition, the sponsor also performed an open-label, single-center, multiple-dose study to evaluate the concentration of meropenem in plasma and cantharidin-induced skin blisters to support the findings from the Phase 3 comparative clinical study.

1.1. RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III (OCPB/DPE-III) has reviewed NDA 50-706/SE1-018 and it is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

The proposed labeling changes in Section 4.1 were communicated to the sponsor. The sponsor responded on May 16, 2005 with minor revisions to the recommended dosage schedule for adults with impaired renal function table and recommended dosage schedule for pediatrics with normal renal function table. The labeling changes were acceptable.

1.2. PHASE IV COMMITMENTS:

No Phase IV commitments are recommended.

1.3. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The sponsor conducted an open-label, single-center, multiple-dose study to evaluate the concentration of meropenem in plasma and cantharidin-induced skin blisters in order to support the clinical efficacy of meropenem as single agent therapy for cSSSI. Ten healthy male subjects received meropenem 500 mg IV every 8 hrs infused over 30 min for three doses. Prior to the 3rd dose of meropenem, each subject had six skin blisters raised on their forearms. Corresponding plasma and skin blister fluid samples were obtained after the 3rd dose of meropenem for 12 hrs.

Meropenem plasma and skin blister fluid concentrations were similar at approximately 2 hrs and skin blister fluid concentrations exceeded plasma concentrations after 2 hrs. The mean (CV%) C_{max} of meropenem in plasma was 24.0 (18%) µg/mL and observed at the end of the 30 minute infusion. The mean (CV%) C_{max} of meropenem in skin blister fluid was 5.5 (35%) µg/mL and occurred at 1.22 hrs (range 0.50 to 2.0 hrs) after the start of the infusion. The mean skin blister fluid AUC_{0-t} was 18.6 µg*hr/mL and represented 66.8% of the mean plasma AUC_{0-t} (28.2 µg*hr/mL).

The PK/PD parameter that has been shown to best correlate with the efficacy of β-lactam antibiotics is the percentage of the dosing interval in which the plasma concentration remains above the minimum inhibitory concentration (T >MIC). Thus, the T >MIC of meropenem concentrations in plasma and skin blister fluid was calculated using a MIC upper limit of 4 µg/mL (susceptibility breakpoint of meropenem for aerobic organisms other than *Haemophilus* spp. and Streptococci). The results are shown in Table 1.

Table 1. Mean (range) T >MIC for meropenem in plasma and skin blister fluid

MIC value	T >MIC (%)	
	Plasma (n=8)	Blister Fluid (n=9)
0.125	90% (70-100%)	100% (100%)
0.25	77% (61-87%)	97% (88-100%)
0.5	64% (52-72%)	94% (73-100%)
1	51% (43-56%)	78% (55-93%)
2	39% (34-43%)	51% (34-68%)
4	27% (25-31%)	14% (0-43%)

Based on recently published susceptibility data (Diagn. Microbiol. Infect. Dis. 2004;49:273-281), the MIC_{90} values for oxacillin-susceptible *Staphylococcus aureus*, coagulase-negative staphylococci, and Streptococcus spp. (including β-haemolytic Streptococcus spp., viridans group Streptococci, and *Streptococcus bovis*) were ≤0.12 μg/mL. Thus, the concentration of meropenem in skin blister fluid should exceed the MICs of typical pathogens relevant to complicated skin and skin structure infections for the entire dosing interval. The skin blister study supports the results from the Phase 3 clinical study that meropenem 500 mg q8h should be effective in the treatment of complicated skin and skin structure infections.

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cc:
Division File: NDA 50-706
HFD-520 (CSO/Samanta)
HFD-520 (MO/Mulinde, Smith)
HFD-880 (Division File, Lazor, Selen, Jarugula, Bonapace)
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