CLINICAL EFFICACY

COMPLICATED URINARY TRACT INFECTION (cUTI)

The Applicant submits the protocols and results of two studies (**DORI-05 and DORI-06)** performed to support the indication for cUTI.

DORI-05: A Multicenter, Double-Blind, Randomized, Phase 3 Study to Compare the Safety and Efficacy of Intravenous Doripenem and Levofloxacin in Complicated Lower Urinary Tract Infection or Pyelonephritis

STUDY PROTOCOL

Number of Study Centers

A total of 44 centers (18 in the United States, 7 in Germany, 7 in Argentina, 6 in Brazil, 5 in Poland, and 1 in Canada) randomized 753 patients in this study.

Primary Objective

- To determine the microbiological response at the Test-of-cure (TOC) visit (6 to 9 days after the completion of study drug therapy) in patients with complicated lower urinary tract infections (cLUTI) and pyelonephritis following a 10-day treatment regimen. [Here, "cUTI" refers to both complicated lower urinary tract infection (cLUTI) and pyelonephritis.]

Secondary Objective

- To determine the clinical response at the TOC visit (6 to 9 days after the completion of study drug therapy) in patients with cUTI following a 10-day treatment regimen.

Study Design

This was a Phase 3, multicenter, prospective, randomized, double-blind study of doripenem, administered as a 1-hour IV infusion (500 mg q8h), versus levofloxacin, administered as a 1-hour IV infusion (250 mg q24h), in the treatment of cUTI in adults. The study was blinded using either placebo levofloxacin q24h for patients receiving active doripenem or placebo doripenem q8h for patients receiving active levofloxacin.

Randomization was stratified by region (North America, South America, or Europe) and within each region by baseline diagnosis (symptomatic cLUTI, asymptomatic cLUTI, or pyelonephritis). Urine specimens for culture were collected at screening (within 48 hours prior to administration of the first dose of study drug therapy). Catheterized patients from whom the urine specimen was obtained through the catheter, patients who presented with pyelonephritis, and patients who were suspected to have bacteremia had blood samples drawn for culture.

After six or more doses (approximately 48 hours) of IV study drug therapy had been given during hospitalization, patients were allowed to be discharged if arrangements had been made for continued IV administration of study drug therapy and the collection of all required study assessments. After nine or more doses of IV study drug therapy, patients could have switched to oral levofloxacin tablets (250 mg PO q24h) if no fever (< 37.8°C oral) was noted for at least 24 hours; if signs, symptoms or both of cUTI were absent or improved relative to those before the start of IV study drug therapy; and one or more urine cultures had been reported with no growth at 24 hours or growth with a colony count of $< 10^4$ CFU/mL and no known subsequent cultures with a colony count of $= 10^4$ CFU/mL were observed.

Number of Patients (planned and analyzed)
750 planned (375 per treatment arm); 753 randomized (377 doripenem, 376 levofloxacin); 748 received study drug therapy (ITT or safety: 376 doripenem, 372 levofloxacin); 545 were microbiologically evaluable (ME) at TOC (280 doripenem, 265 levofloxacin); and 648 were microbiological modified ITT (mMITT) (327 doripenem, 321 levofloxacin) of cUTI and with a pre-treatment baseline urine culture obtained within 48 hours prior to the start of administration of the first dose of study drug therapy from which a bacterial uropathogen was isolated with a growth of $= 10^5$ CFU/mL were eligible.

Test Product, Dose and Mode of Administration
Doripenem for Injection 500 mg given by IV infusion over one hour.

Duration of Treatment
10 days (IV and oral)

Reference Therapy, Dose, and Mode of Administration
Levofloxacin Injection 250 mg given by IV infusion over 1 hour.

Criteria for Efficacy Evaluation
The primary endpoint was the per-patient microbiological cure rate (i.e., eradication of all baseline uropathogens) at the TOC visit (5 to 11 days post-therapy) in the ME at TOC and mMITT analysis sets.

The secondary efficacy endpoint was clinical cure rates (i.e., cure) at the TOC visit and per baseline uropathogen microbiological outcomes (eradicated or not eradicated) for *Escherichia coli* at the TOC visit.

DORI-06: A Multicenter, Phase 3 Study to Confirm the Safety and Efficacy of Intravenous Doripenem in Complicated Lower Urinary Tract Infection or Pyelonephritis

Number of Study Centers
A total of 30 centers (11 in the United States, 9 in Argentina; 6 in Brazil, 3 in Austria, and 1 in Canada) enrolled 426 patients in this study.

Primary Objective
- To determine the microbiological response at the test-of-cure (TOC) visit (6 to 9 days after the completion of study drug therapy) in patients with complicated lower urinary tract infections (cLUTI) and pyelonephritis* following a 10-day treatment regimen.

Secondary Objectives
- To determine the clinical response at the TOC visit (6 to 9 days after completion of study drug therapy) in patients with cUTI following a 10-day treatment regimen.

Study Design
This was a Phase 3, multicenter, prospective, open-label, single arm study of doripenem, administered as a 1-hour intravenous (IV) infusion (500 mg every 8 hours [q8h]) in the treatment of cUTI in adults. Urine specimens for culture were collected at Screening (within 48 hours prior to administration of the first dose of study drug therapy). Catheterized patients from whom the urine specimen was obtained through the catheter, patients who presented with pyelonephritis, and patients who were suspected to have bacteremia had blood samples drawn for culture.

After at least 6 doses (approximately 48 hours) of IV study drug therapy had been administered while patients were hospitalized, the patients could have been discharged from the hospital if arrangements were made for continued IV administration of study drug therapy and the collection of all required study assessments. After 9 or more doses of IV study drug therapy, patients could have switched to levofloxacin tablets 250 mg orally q24h if no fever (oral temperature less than 37.8°C) was noted for at least 24 hours; if signs and/or symptoms of cUTI were absent or improved relative to those before the start of IV study drug therapy; and at least one urine culture had been reported with no growth at 24 hours or growth with a colony count of less than 10^4 colony-forming units (CFU)/mL and no known subsequent cultures with a colony count of greater than or equal to 10^4 CFU/mL were observed.

Number of Patients (planned and analyzed)
450 planned; 426 enrolled, 423 received at least 1 dose of IV study drug therapy (Intent-to-Treat [ITT]); 250 were microbiologically evaluable (ME) at TOC, 337 were part of the microbiological modified ITT (mMITT) analysis set.

Diagnosis and Main Criteria for Inclusion
Male or female patients aged 18 years or older with clinical signs and/or symptoms of cUTI and with a pre-treatment baseline urine culture obtained within 48 hours prior to the

start of administration of the first dose of study drug therapy from which a bacterial uropathogen was isolated with a growth of greater than or equal to 10^5 CFU/mL were eligible.

Test Product, Dose and Mode of Administration
Doripenem for Injection 500 mg administered by IV infusion over 1 hour q8h.

Duration of Treatment: 10 days (IV and oral)

Reference Therapy, Dose, and Mode of Administration: None

Criteria for Efficacy Evaluation
The primary efficacy endpoint was the per-patient microbiological cure (i.e., eradication of all baseline pathogens) rates at the TOC (6-9 days post-therapy) in the ME at TOC and mMITT analysis sets.

The secondary efficacy endpoints included the clinical cure rates at the TOC visit and the per baseline uropathogen microbiological outcomes (eradicated or not eradicated) at the TOC visit. Safety was assessed through monitoring of adverse events (AEs), physical examination, vital sign measurements, and laboratory data (serum chemistries, hematology, and urinalysis).

DORI-06: A Multicenter, Phase 3 Study to Confirm the Safety and Efficacy of Intravenous Doripenem in Complicated Lower Urinary Tract Infection or Pyelonephritis

Number of Study Centers
A total of 30 centers (11 in the United States, 9 in Argentina; 6 in Brazil, 3 in Austria, and 1 in Canada) enrolled 426 patients in this study.

Primary Objective
- To determine the microbiological response at the test-of-cure (TOC) visit (6 to 9 days after the completion of study drug therapy) in patients with complicated lower urinary tract infections (cLUTI) and pyelonephritis* following a 10-day treatment regimen.

Secondary Objectives
- To determine the clinical response at the TOC visit (6 to 9 days after completion of study drug therapy) in patients with cUTI following a 10-day treatment regimen.

Study Design
This was a Phase 3, multicenter, prospective, open-label, single arm study of doripenem, administered as a 1-hour intravenous (IV) infusion (500 mg every 8 hours [q8h]) in the

treatment of cUTI in adults. Urine specimens for culture were collected at Screening (within 48 hours prior to administration of the first dose of study drug therapy). Catheterized patients from whom the urine specimen was obtained through the catheter, patients who presented with pyelonephritis, and patients who were suspected to have bacteremia had blood samples drawn for culture.

After at least six doses (approximately 48 hours) of IV study drug therapy had been administered while patients were hospitalized, the patients could have been discharged from the hospital if arrangements were made for continued IV administration of study drug therapy and the collection of all required study assessments. After nine or more doses of IV study drug therapy, patients could have switched to levofloxacin tablets 250 mg orally q24h if no fever (oral temperature less than 37.8°C) was noted for at least 24 hours; if signs and/or symptoms of cUTI were absent or improved relative to those before the start of IV study drug therapy; and at least one urine culture had been reported with no growth at 24 hours or growth with a colony count of less than 10^4 CFU/mL and no known subsequent cultures with a colony count of greater than or equal to 10^4 CFU/mL were observed.

Number of Patients (planned and analyzed)
450 planned; 426 enrolled, 423 received at least one dose of IV study drug therapy (Intent-to-Treat [ITT]); 250 were microbiologically evaluable (ME) at TOC, 337 were part of the microbiological modified ITT (mMITT) analysis set.

Diagnosis and Main Criteria for Inclusion
Male or female patients aged 18 years or older with clinical signs and/or symptoms of cUTI and with a pre-treatment baseline urine culture obtained within 48 hours prior to the start of administration of the first dose of study drug therapy from which a bacterial uropathogen was isolated with a growth of greater than or equal to 10^5 CFU/mL were eligible.

Test Product, Dose and Mode of Administration
Doripenem for Injection 500 mg administered by IV infusion over 1 hour q8h.

Duration of Treatment: 10 days (IV and oral)

Reference Therapy, Dose, and Mode of Administration: None

Criteria for Efficacy Evaluation
The primary efficacy endpoint was the per-patient microbiological cure (i.e., eradication of all baseline pathogens) rates at the TOC (6-9 days post-therapy) in the ME at TOC and mMITT analysis sets.

The secondary efficacy endpoints included the clinical cure rates at the TOC visit and the per baseline uropathogen microbiological outcomes (eradicated or not eradicated) at the

TOC visit. Safety was assessed through monitoring of adverse events (AEs), physical examination, vital sign measurements, and laboratory data (serum chemistries, hematology, and urinalysis).

CLINICAL MICROBIOLOGY PROTOCOLS

Local Laboratory Procedures

Note: Organism identity and susceptibility in the analyses were based on the central laboratory data and local (or regional) laboratory data were recorded on the CRFs but were generally superseded by the central lab results.

Specimen collection and culture methods

Acceptable methods of urine collection were: 1) a midstream clean catch (preferably a first-voided morning specimen; 2) cauterization, and 3) suprapubic aspiration. Foley catheter tips were not to be accepted for culture due to contamination with urethral organisms. If a specimen was collected from a catheter, the catheter had to be disinfected and then punctured in the disinfected area with a needle to collect a specimen. All urine specimens were to be transported to the laboratory promptly and processed within 2 hours of collection. If a delay in transport or processing could be avoided, specimens were to be refrigerated for up to 24 hours. Cultures were to be initiated as usual per local laboratory procedures for standard bacterial culture, anaerobic culture, mycobacterial or fungal culture, as appropriate.

For all patients: A study-qualifying pretreatment baseline urine culture was defined as growth of at least one and not more than two uropathogens at $=10^5$ CFU/mL. If two uropathogens were isolated with a growth of $=10^5$ CFU/mL, both were considered causative pathogens. If more than two organisms were isolated, the culture was considered contaminated regardless of colony count unless one of the organisms that grew in the urine at $=10^5$ CFU/mL grew in a simultaneously obtained blood culture. Coagulase negative staphylococci and non-Group D streptococci were not considered etiologic pathogens in cUTI in this study.

For catheterized patients: Patients who were catheterized were required to have pretreatment baseline blood cultures (one aerobic bottle from each of two separate sites for a total of two aerobic bottles per draw) obtained at the time the baseline urine culture specimen was provided. A catheter was defined as any tube, stent or foreign body conduit that extends from the inside the body to the outside of the body. If a catheterized patient's urine grew more than one organism at any concentration, the urine culture was to be considered contaminated unless the blood culture also grew one of the uropathogens present in the urine at $=10^5$ CFU/mL. Blood samples for culture were processed as per the usual procedures at each site's local laboratory. Both aerobic and anaerobic blood cultures were to be performed. All isolates from blood cultures (whether pathogens or contaminants) from positive cultures were to be sent to the sponsor-designated central laboratory for confirmation of identification and susceptibility testing.

Microscopic evaluation of specimens
Gram stain examination criteria to determine quality of specimens was not defined in the protocol. Site laboratories followed their local procedures.

Organism identification methods
Study site laboratories identified pathogens as usual per local laboratory procedures.

Interpretive criteria at the local laboratories
No susceptibility testing was required for doripenem at the site, therefore, no interpretive criteria were provided. Levofloxacin achieves high levels in urine. As the result patients were managed based on signs and symptoms rather than using breakpoints, which have been determined primarily based on serum levels. Therefore, sites were not specifically provided with CLSI interpretative criteria for levofloxacin and susceptibility tests were not done.

Sample Storage and Shipment
All clinical specimens were to be processed at the site's local laboratory and the results of these were recorded on the Case Report Form (CRF). All potential pathogens were to be stored at –70° C in cryovials for shipment to the central laboratory, which was to occur as soon as feasible. If storage at -70° C was not possible, TSBS tubes were provided for storage at -20°C until shipping to the central laboratory.

Central Laboratory Procedures
Susceptibility testing methods
The central laboratory followed CLSI methodologies or manufacturer's instructions for susceptibility testing. Susceptibility testing was done for doripenem and comparator agents. A list of agents for which MIC testing was performed in the central laboratory is included below.

Gram-negative organisms: amikacin, ampicillin, ampicillin/ sulbactam, aztreonam, cefazolin, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, doripenem, ertapenem, imipenem, levofloxacin, meropenem, piperacillin/ tazobactam, tetracycline, tobramycin and trimethoprim/ sulfamethoxazole.

Gram-positive organisms: ampicillin, ceftazidime, ceftriaxone, ciprofloxacin, clindamycin, daptomycin, doripenem, ertapenem, erythromycin, gentamicin, imipenem, levofloxacin, linezolid, meropenem, oxacillin, penicillin, piperacillin/ tazobactam, rifampin, teicoplanin, telithromycin, trimethoprim/ sulfamethoxazole and vancomycin.

For the purpose of this study, doripenem MIC interpretative criteria were MIC = 4 µg/ml (susceptible); MIC = 8 µg/ml (intermediate-susceptible); MIC = 16 µg/ml (resistant). For other comparators susceptibility results were interpreted as per Clinical Laboratory Standards Institute (CLSI) standards. Disk susceptibility was performed for doripenem,

imipenem and meropenem and the criteria below were used for doripenem zone interpretation.

Table 38. Doripenem "Study Specific" Interpretative Criteria

Isolate	Method	Zone Diameter	Interpretation
Pseudomonas aeruginosa and other non-fermenters	Disk Diffusion	< 17 mm	Resistant
Enterobacteriaceae	Disk Diffusion	< 17 mm	Resistant
Staphylococcus aureus	Methicillin Resistance Screening	--	Oxacillin or cefoxitin resistant strains should be considered resistant to doripenem
	Oxacillin-Salt Agar Screen or	Growth, > 1 colony	Resistant
	Oxacillin Disk (1 µg disk)	≤ 10 mm	Resistant
	Cefoxitin Disk (30 mg disk)	≤ 19 mm	Resistant, report as oxacillin resistant
Enterococcus faecalis	Ampicillin	≤16 mm	Resistant Ampicillin-resistant strains should be considered resistant to doripenem
Enterococcus faecium	--	--	All isolates are assumed to be resistant to doripenem
Streptococci	Disk Diffusion	< 17 mm	Resistant
Anaerobes	--	--	All isolates are assumed to be resistant to doripenem

CLSI has approved quality control zone size limit ranges for disk diffusion testing for doripenem. These limits are presented in the table below.

Table 39. Quality Control Zone Size Limit Ranges for Doripenem

Organism	Zone Size Limit in mm
S. aureus ATCC25923	33-42
E. coli ATCC25922	28-35
P. aeruginosa ATCC 27853	29-35
S. pneumoniae ATCC49619	30-38

CORRELATION OF MIC AND CLINICAL AND MICROBIOLOGIC OUTCOME

A summary table is provided in Table 40 showing both the clinical cure and bacteriologic eradication rates for patients infected with each of the pathogens causing complicated urinary tract infections (cUTI).

Table 40. Clinical and Bacteriologic Outcome by Pathogen (cUTI)

Organism	Doripenem Clinical Cure (%)	Doripenem Bacterial Eradication (%)	Levofloxacin Clinical Cure (%)	Levofloxacin Bacterial Eradication (%)
Gram-negative aerobes				
Acinetobacter baumannii	10/10 (100)	8/10 (80)	0/1 (0)	0/1 (0)
Enterobacter cloacae	22/28 (79)	18/28 (64)	3/7 (43)	3/7 (43)
Escherichia coli	341/350 (97)	313/357 (88)	191/204 (94)	184/211 (87)
Klebsiella pneumoniae	29/32 (91)	26/33 (79)	4/7 (57)	5/8 (63)
Proteus mirabilis	29/30 (97)	22/30 (73)	13/15 (87)	13/15 (87)
Pseudomonas aeruginosa	23/24 (96)	17/24 (71)	5/6 (83)	5/7 (71)
Gram-positive aerobes				
Enterococcus faecalis	10/12 (83)	8/12 (67)	2/2 (100)	1/3 (33)

Source: Tables TEFF108, 111, 112, 113, 127 and 129, Response to Microbiology questions, this submission.

Gram-negative bacteria

The Applicant seeks label claims for three Gram-negative pathogens including *A. baumannii,* — *E. coli, K. pneumoniae, P. mirabilis* and *P. aeruginosa.* Compared to levofloxacin treated patients, doripenem treated patients had higher clinical cure, bacteriologic eradication rates or both for patients infected with any one of the Gram-negative aerobes.

Patients infected with *E. coli* and treated with doripenem had clinical cure and bacteriologic eradication rates of 97% and 88%, respectively, while patients treated with levofloxacin had clinical cure and bacteriologic eradication rates of 94% and 87%, respectively, indicating differences of 3% and 1%, respectively. **Consequently, this Reviewer recommends the Applicant be granted claims for *E. coli.***

Patients infected with *K. pneumoniae* and treated with doripenem had clinical cure and bacteriologic eradication rates of 91% and 79%, respectively, while patients treated with levofloxacin had clinical cure and bacteriologic eradication rates of 57% and 63% representing differences of 34% for clinical cure and 16% for bacteriologic eradication. Thus, **this Reviewer recommends that the Applicant be granted claims for *K. pneumoniae.***

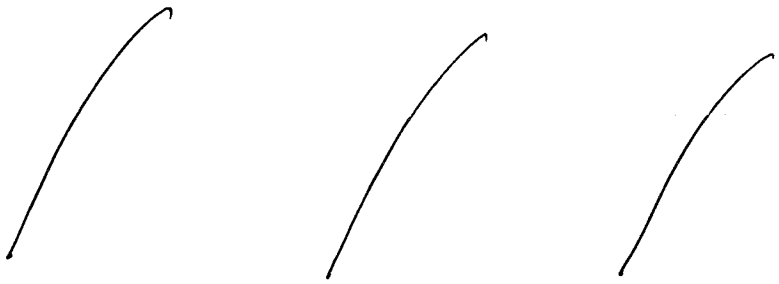
Patients infected with *A. baumannii* and treated with doripenem had clinical cure and bacteriologic eradication rates of 100% and 80%, respectively, while patients treated with levofloxacin had clinical cure and bacteriologic eradication rates of 0% representing

differences of 100% for clinical cure and 80% for bacteriologic eradication. However, there was only one patient in the levofloxacin arm. Thus, **this Reviewer recommends that the Applicant be granted claims for *A. baumannii.***

Patients infected with *P. aeruginosa* and treated with doripenem had clinical cure and bacteriologic eradication rates of 96% and 71%, respectively, while patients treated with levofloxacin had clinical cure and bacteriologic eradication rates of 83% and 71%, respectively; these represent differences of 13% for clinical cure and 0% for bacteriologic eradication rates. However, Monte Carlo simulation data (see Table 31) indicate that the probability of target attainment is below the range considered relevant to *in vivo* efficacy (≥ 80%) in some cases. During one-hour infusions of 500 mg, q8h, non-*Enterobacteriaceae* attained 25%, 30% and 35% T>MIC for 83.6, 80.7 and 77.7 %, respectively. Thus, **this Reviewer recommends that the Applicant be granted claims for *P. aeruginosa.***

Patients infected with *P. mirabilis* and treated with doripenem had clinical cure and bacteriologic eradication rates of 97% and 73%, respectively, while patients treated with levofloxacin had clinical cure and bacteriologic eradication rates of 87% representing differences of 10% for clinical cure and 14% for bacteriologic eradication. However, Levo Floxin demonstrated a greater bacteriologic eradication rate (87%) than doripenem (73%) which is the primary measure of efficacy for cUTI. Thus, **this Reviewer recommends that the Applicant be granted claims for *P. mirabilis.***

Gram-positive bacteria
The Applicant seeks label claims for one Gram-positive pathogen. [redacted]



The Applicant presents the results of clinical cure and bacteriologic eradications rates for patients infected with different Gram-negative organisms stratified by different doripenem MICs in Table 41.

Table 41. Per Pathogen Clinical Outcome at TOC by Baseline Doripenem MIC Level for cUTI

Organism/Baseline Doripenem MIC (µg/ml)	N	Clinical Cure (%)	Bacterial Eradication (%)
Gram-negative aerobes			
[redacted]			
0.12		1/1 (100)	1/1 (100)
0.25		1/1 (100)	1/1 (100)
0.5		1/1 (100)	1/1 (100)
1		6/6 (100)	5/6 (83)
2		1/1 (100)	1/1 (100)
[redacted]			
≤ 0.03		3/5 (60)	3/5 (60)
0.06		4/5 (80)	3/5 (60)
0.12		3/4 (75)	2/4 (50)
0.25		2/2 (100)	2/2 (100)
0.5		9/11 (82)	8/11 (73)
1		1/1 (100)	0/1 (0)
[redacted]			
≤ 0.03		297/304 (98)	271/308 (88)
0.06		25/27 (93)	24/30 (80)
0.12		4/4 (100)	3/4 (75)
[redacted]			
≤ 0.03		7/7 (100)	8/8 (100)
0.06		10/10 (100)	10/10 (100)
0.12		5/6 (83)	3/6 (50)
0.25		0/2 (0)	1/2 (50)
0.5		1/1 (100)	0/1 (0)
[redacted]			
≤ 0.03		1/1 (100)	0/1 (0)
0.06		2/2 (100)	1/2 (50)
0.12		10/10 (100)	8/10 (80)
0.25		9/9 (100)	7/9 (78)
0.5		7/8 (88)	6/8 (75)
[redacted]			
≤ 0.03		1/1 (100)	ND
0.06		1/1 (100)	ND
0.12		2/2 (100)	ND
0.25		3/3 (100)	6/7 (86)*
0.5		4/4 (100)	2/4 (50)
1		4/4 (100)	3/4 (75)
2		3/3 (100)	2/3 (67)
4		1/1 (100)	1/1 (100)
8		2/3 (67)	2/3 (67)
16		2/2 (100)	1/2 (50)

Source: Tables TEFF108, 111, 112 and 113, Response to Microbiology questions, this submission.

The Applicant presents data from cUTI studies showing the clinical and microbiologic outcomes at each MIC for Gram-negative organisms including: *A. baumannii, E. cloacae, E. coli, K. pneumoniae, P. mirabilis* and *P. aeruginosa.* Ninety percent (9/10) of the *A. baumannii* isolates had a MIC of ≤ 1 µg/ml which was also the MIC mode. All of these isolates had a MIC value of ≤ 2 µg/ml. Among *E. cloacae* isolates, 93% (27/29) had a MIC value of ≤ 0.5 µg/ml which was also the MIC mode. All of these isolates had a MIC value of ≤ 1 µg/ml. Among *E. coli* isolates, 90% (301/335) had a MIC value of ≤ 0.03 µg/ml which was also the MIC mode. All of these isolates had a MIC value of ≤ 0.12 µg/ml. Eighty-eight percent (23/26) of the *K. pneumoniae* isolates had a MIC of ≤ 0.12 µg/ml. The mode MIC was 0.06 µg/ml. Among *P. mirabilis* isolates, 90% (27/30) had MIC values of 0.12— 0.5 µg/ml. Among *P. aeruginosa* isolates, 92% (22/24) had MICs ≤ 8 µg/ml. MIC values were evenly distributed across a range of ≤ 0.03 and 16 µg/ml. Among *E. coli* and *P. aeruginosa* isolates, the two species deemed adequate for inclusion in the label claims, MIC values were quite different between the two organisms. Just as was seen among these pathogens in the cIAI trial, the mode MIC among *E. coli* isolates was ≤ 0.03 µg/ml, MICs among *P. aeruginosa* isolates were relatively evenly distributed.

. Overall, there was little correlation of MIC with clinical or bacteriologic outcome.

The Applicant presents the results of clinical cure and bacteriologic eradications rates for patients infected with different Gram-positive bacteria stratified by different doripenem MICs in Table 42.

Table 42. Per Pathogen Clinical Outcome at TOC by Baseline Doripenem MIC Level for cUTI

Organism/Baseline Doripenem MIC (µg/ml)	N	Clinical Cure (%)	Bacterial Eradication (%)
Gram-positive bacteria			
Enterococcus faecalis	12	10/12 (83)	8/12 (67)
≤ 0.03		1/1 (100)	ND
0.12		1/1 (100)	ND
0.25		1/1 (100)	3/3 (100)*
0.5		1/1 (100)	0
1		1/1 (100)	0/1 (0)
2		2/3 (67)	3/3 (100)
4		4/4 (100)	2/4 (50)
16		0/1 (0)	0/1 (0)

Source: Tables TEFF108, 111, 112 and 113, Response to Microbiology questions, this submission.

The Applicant presents data from cUTI studies showing the clinical and microbiologic outcomes at each MIC for one Gram-positive aerobic organism, namely *E. faecalis.* About 92% (11/12) of the *E. faecalis* isolates had a MIC of ≤ 4 µg/ml. Most isolates had

a MIC value of either 2 or 4 µg/ml. Again, there was little correlation of MIC with clinical or bacteriologic outcome.

COMPLICATED INTRA-ABDOMINAL INFECTIONS (cIAI)

The Applicant submits the protocols and results of two studies (**DORI-07 and DORI-08)** performed to support the indication for cIAI.

DORI-07: A Multicenter, Double-Blind, Randomized, Phase 3 Study to Compare the Safety and Efficacy of Intravenous Doripenem with that of Meropenem in Complicated Intra-abdominal Infections

STUDY PROTOCOL

Number of Study Centers

A total of 46 centers (23 in the United States, 7 in Argentina, 5 in Brazil, 5 in Germany, 5 in Poland, and 1 in Canada) randomized 476 patients in this study.

Primary Objective

To compare the clinical response of doripenem vs. meropenem in hospitalized patients with complicated intra-abdominal infections (cIAI) at the Test-of-cure (TOC) visit (4 to 6 weeks after the completion of study drug therapy).

Secondary Objectives

To compare:

- the microbiological response at the TOC visit;
- the clinical response at the early follow-up (EFU) (1 to 2 weeks after treatment) and end of IV therapy (EOT[IV]) visits;
- the microbiological response at the EFU and EOT(IV) visits; and 4) the safety profile of doripenem with that of meropenem.

Study Design

This was a Phase 3, multicenter, prospective, randomized, double-blind, double-dummy study of doripenem, administered as a 1-hour IV infusion (500 mg q8h) vs. meropenem, administered as a 3- to 5-minute IV bolus (1 g q8h) in the treatment of cIAI in adults. The study was blinded using either placebo meropenem for patients receiving doripenem or placebo doripenem for patients receiving meropenem.

Randomization was stratified by region (North America, South America, or Europe) and within each region by primary site of infection (complicated localized appendicitis vs. diagnosis of other sites of intra-abdominal infections [IAIs]) and severity of illness (APACHE II score = 10 or > 10).

Intra-abdominal culture specimens (both aerobic and anaerobic) were collected at the time of the initial procedure (within 24 hours of enrollment). Blood culture samples were drawn from all patients.

After six or more doses (approximately 48 hours) of IV study drug therapy had been given during hospitalization, the patients were discharged if arrangements had been made for continued IV administration of study drug therapy and the collection of all required study assessments. After nine or more doses of IV study drug therapy (or equivalent if dose adjusted for renal impairment), patients could have been switched to oral amoxicillin/clavulanate therapy (875/125 mg twice daily) if the following criteria were met: temperature and WBC count were decreasing relative to baseline values (if increased at baseline); cIAI signs and/or symptoms were absent/improved relative to those at baseline; and normal bowel function had returned.

Number of Patients (planned and analyzed)
472 planned (236 per treatment arm); 476 randomized (237 doripenem, 239 meropenem), 471 received study drug therapy (ITT or safety; 235 doripenem, 236 meropenem); 319 were microbiologically evaluable (ME) at TOC (163 doripenem, 156 meropenem); and 385 were included in the microbiological modified ITT (mMITT) analysis set (195 doripenem, 190 meropenem).

Diagnosis and Main Criteria for Inclusion
Male and female patients = 18 years with clinical evidence of IAI, and with planned/recent (within 24 hours) operative/percutaneous drainage of an infection focus, confirming the presence of cIAI.

Test Product, Dose, and Mode of Administration
Doripenem for Injection 500 mg given by IV infusion over 1 hour q8h.

Duration of Treatment
5 to 14 days (IV only or IV plus oral)

Reference Therapy, Dose, and Mode of Administration
Meropenem 1 g given by IV bolus over 3-5 min q8h.

Criteria for Efficacy Evaluation
Primary efficacy endpoints included clinical cure rate at TOC (21-60 days post-therapy) in the ME at TOC analysis set and the clinical cure rate occurring up to 60 days after the last dose of study drug therapy in the mMITT analysis set.
Secondary efficacy endpoints included clinical cure or improvement rates at the EOT(IV) visit, clinical cure rates at the EFU visit (6-20 days post-therapy), and per-patient microbiological cure rates (i.e., eradication or presumed eradication of all baseline pathogens) and per-pathogen microbiological outcomes (i.e. eradication or presumed eradication) at the EFU and TOC visits.

DORI-08: A Multicenter, Double-Blind, Randomized, Phase 3 Study to Compare the Safety and Efficacy of Intravenous Doripenem with that of Meropenem in Complicated Intra-abdominal Infections

Number of Study Centers
A total of 44 centers (21 in the United States, 10 in Europe, 10 in South America, and 3 in Canada) randomized 486 patients in this study.

Primary Objective
To compare the clinical response of doripenem vs. meropenem in hospitalized patients with complicated intra-abdominal infections (cIAI) at the test-of-cure (TOC) visit (4 to 6 weeks after the completion of study drug therapy).

Secondary Objectives
To compare:

- the microbiological response at the TOC visit;
- the clinical response at the early follow-up (EFU) (1 to 2 weeks after treatment) and end of IV therapy (EOT[IV]) visits;
- the microbiological response at the EFU visit; and the safety profile of doripenem with that of meropenem.

Study Center
This was a Phase 3, multicenter, prospective, randomized, double-blind, double-dummy study of doripenem, administered as a 1-hour IV infusion (500 mg q8h) vs. meropenem, administered as a 3- to 5-minute IV bolus (1 g q8h) in the treatment of cIAI in adults. The study was blinded using either placebo meropenem for patients receiving doripenem or placebo doripenem for patients receiving meropenem.

Randomization was stratified by region (North America, South America, or Europe) and within each region by primary site of infection (complicated localized appendicitis vs. diagnosis of other sites of intra-abdominal infections [IAIs]) and severity of illness.

Intra-abdominal culture specimens (both facultative and anaerobic) were collected at the time of the initial procedure (within 24 hours of enrollment). Blood culture samples were drawn from all patients.

After six or more doses (approximately 48 hours) of IV study drug therapy had been given during hospitalization, the patients were discharged if arrangements had been made for continued IV administration of study drug therapy and the collection of all required study assessments. After nine or more doses of IV study drug therapy (or equivalent if dose adjusted for renal impairment), patients could have switched to oral amoxicillin/clavulanate therapy (875/125 mg twice daily) if the following criteria were met: temperature and WBC count were decreasing relative to baseline values (if

increased at baseline); cIAI signs and/or symptoms were absent/improved relative to those at baseline; and normal bowel function had returned.

Number of Patients (planned and analyzed)
472 planned (236 per treatment arm); 486 randomized (249 doripenem, 237 meropenem), 475 received study drug therapy (ITT or safety; 242 doripenem, 233 meropenem); 315 were microbiologically evaluable (ME) at TOC (162 doripenem, 153 meropenem); and 385 were included in the microbiological modified ITT (mMITT) analysis set (200 doripenem, 185 meropenem).

Diagnosis and Main Criteria for Inclusion
Male and female patients' $\geq$ 18 years with clinical evidence of IAI, and with planned/recent (within 24 hours) operative/percutaneous drainage of an infection focus, confirming the presence of cIAI.

Test Product, Dose, and Mode of Administration
Doripenem for Injection 500 mg given by IV infusion over 1 hour q8h.

Duration of Treatment
5 to 14 days (IV only or IV plus oral)

Reference Therapy, Dose, and Mode of Administration
Meropenem 1 g given by IV bolus over 3-5 min q8h.

Criteria for Efficacy Evaluation
Primary efficacy endpoints included clinical cure rate at TOC (21-60 days post-therapy) in the ME at TOC analysis set and the clinical cure rate at any time up to 60 days after the last dose of study drug therapy in the mMITT analysis set.

Secondary efficacy endpoints included clinical cure or improvement rates at the EOT(IV) visit, clinical cure rates at the EFU visit (6-20 days post-therapy), and per-patient microbiological cure rates (i.e., eradication or presumed eradication of all baseline pathogens) and per-pathogen microbiological outcomes (i.e., eradication or presumed eradication) at the EFU and TOC visits.

CLINICAL MICROBIOLOGY PROTOCOLS

Local Laboratory Procedures
Note: Organism identity and susceptibility in the analyses were based on the central laboratory data and local (or regional) laboratory data were recorded on the CRFs but were generally superseded by the central lab results.

Specimen collection and culture methods
Intra-abdominal or blood cultures were to be processed at the site local laboratory in less than two hours. However, if the site local laboratory was not available or not suitable for

processing the sample, the specimen was placed in transport medium and sent at ambient temperature to a sponsor-designated regional central laboratory for adequate processing. Regional central laboratories were — in Argentina; — in Brazil; — in Germany; — in Poland. Collection tubes with transport medium were provided to sites for shipping of specimens to a regional central laboratory, where they were processed. Specimens were processed as usual per local laboratory procedures for standard bacterial culture, anaerobic culture, mycobacterial or fungal culture, as appropriate.

Intra-abdominal and abdominal wound cultures: Specimens from the intra-abdominal site of infection were obtained at study entry and at subsequent time points as clinically indicated. Specimens from abdominal drains were not to be obtained for study purposes. Note: The method used to transport the specimen to the microbiology laboratory supported the isolation of anaerobes. In the US, both aerobic and anaerobic specimens were obtained and processed in the local laboratory. All pathogens isolated were stored for later shipping to the US central laboratory. At study centers outside the US, specimens were obtained and placed in the provided transport medium and shipped as soon as possible to the country-specific regional laboratory. All isolates obtained at the regional laboratory were later shipped to the US central laboratory.

Blood Cultures: Blood cultures were obtained in all patients at baseline and repeated at any time during the study in patients who had systemic signs suggestive of sepsis (e.g., fever, leukocytosis, tachycardia, decreased blood pressure, etc.) or who were assessed as treatment failures. To obtain an appropriate blood culture, two separate blood samples were drawn and each sample divided into aerobic and anaerobic culture bottles. At all study centers, except in South America, blood cultures were processed in the local laboratory. All blood isolates were stored for future shipping to the US central laboratory. In South America, blood culture bottles were sent to the regional laboratory for processing. If additional blood cultures were sent to the local laboratory, these were processed as per usual procedures and all pathogens stored at the site for later shipping to the US central laboratory.

Other cultures (i.e., not blood, intra-abdominal site or abdominal wound): At any time during the study, cultures obtained from other suspected sites of infection were processed at the study site's local laboratory. All pathogens isolated were stored for later shipping to the US central laboratory.

Microscopic evaluation of specimens
Gram stain examination was not specified as a criterion for specimen suitability. Sites followed their local standard.

Organism identification methods
Pathogens were identified as usual per local laboratory or regional laboratory procedures.

Sample Shipment and Storage
All potential pathogens were stored in duplicate at –70° in cryovials for shipment to the central laboratory. If storage at –70°C was not possible, TSBS tubes were provided for storage at -20°C. Duplicate strains were stored at the local laboratory until the study was completed.

Central Laboratory Procedures
Susceptibility testing methods
The central laboratory followed CLSI methodologies or manufacturer's instructions for susceptibility testing. Susceptibility testing was done for doripenem and comparator agents. A list of agents for which MIC testing was performed in the central laboratory on Gram-negative and Gram-positive organisms is presented in the **CLINICAL MICROBIOLOGY PROTOCOLS** section for the **cUTI** indication.

Bacteroides fragilis group (broth microdilution method): ampicillin/ sulbactam, ceftriaxone, clindamycin, doripenem, imipenem, levofloxacin, meropenem, metronidazole, moxifloxacin and piperacillin/ tazobactam

Non-Bacteroides fragilis and other anaerobes (agar dilution method): doripenem and meropenem

For the purpose of this study, doripenem MIC interpretative criteria were MIC = 4 µg/ml (susceptible); MIC = 8 µg/ml (intermediate-susceptible); MIC = 16 µg/ml (resistant). For other comparators susceptibility results should be interpreted as per Clinical Laboratory Standards Institute (CLSI) standards. Disk susceptibility was performed for doripenem, imipenem and meropenem and the criteria below were used for doripenem zone interpretation.

Doripenem "Study Specific" Interpretative Criteria
These criteria are identical to those presented in the **CLINICAL MICROBIOLOGY PROTOCOLS** section for the **cUTI** indication.

CLSI Published Quality Control Zone Size Limit Ranges for Doripenem
CLSI has approved quality control zone size limit ranges for disk diffusion testing for doripenem. These limits are presented in the same table presented in the **CLINICAL MICROBIOLOGY PROTOCOLS** section for the **cUTI** indication.

CORRELATION OF MIC AND CLINICAL AND MICROBIOLOGIC OUTCOME

A summary table is provided in Table 43 showing both the clinical cure and bacteriologic eradication rates for patients infected with each of the disease causing pathogens sought in the indication.

Table 43. Clinical and Bacteriologic Outcomes in IAI Patients per Pathogen

Organism	Doripenem		Meropenem	
	Clinical Cure (%)	Bacteriologic Eradication (%)	Clinical Cure (%)	Bacteriologic Eradication (%)
Anaerobes				
Bacteroides caccae	22/25 (86)	23/25 (92)	18/19 (95)	18/19 (95)
Bacteroides fragilis	56/67 (84)	56/67 (84)	54/68 (79)	54/68 (79)
Bacteroides thetaiotaomicron	27/34 (79)	30/34 (88)	31/36 (86)	32/36 (89)
Bacteroides uniformis	19/22 (86)	19/22 (86)	15/18 (83)	15/18 (83)
Bacteroides vulgatus	11/11 (100)	11/11 (100)	6/8 (75)	6/8 (75)
Peptostreptococcus micros	9/13 (69)	11/13 (85)	11/14 (79)	11/14 (79)
Gram-negative aerobes				
Escherichia coli	187/216 (87)	189/216 (88)	167/199 (84)	168/199 (84)
Klebsiella pneumoniae	23/32 (72)	25/32 (78)	19/20 (95)	19/20 (95)
Pseudomonas aeruginosa	33/40 (83)	34/40 (85)	25/32 (78)	24/32 (75)
Gram-positive aerobes				
Enterococcus faecalis	15/20 (75)	16/20 (80)	13/17 (76)	13/17 (76)
Streptococcus constellatus	9/10 (90)	9/10 (90)	5/7 (71)	5/7 (71)
Streptococcus intermedius	29/36 (81)	30/36 (83)	20/29 (69)	21/29 (72)

Source: Tables TEFF103, 106, 121 and 124, Response to Microbiology questions, this submission.

Anaerobes

The Applicant seeks label claims for six anaerobic pathogens including *B. caccae, B. fragilis, B. thetaiotaomicron, B. uniformis, B. vulgatus* and *P. micros*. Compared to meropenem treated patients, doripenem treated patients had higher clinical cure and bacteriologic eradication rates for patients infected with either *B. fragilis* or *B. uniformis*. Patients infected with *B. caccae* and treated with doripenem had clinical cure and bacteriologic eradication rates of 86% and 92%, respectively; patients treated with meropenem had clinical cure and bacteriologic eradication rates of 95%, a difference of 9% and 3%, respectively. Patients infected with *B. fragilis* and treated with doripenem had clinical cure and bacteriologic eradication rates of 84% while patients treated with meropenem had clinical cure and bacteriologic eradication rates of 79%, a difference of 5%. Patients infected with *B. thetaiotaomicron* and treated with doripenem had clinical cure and bacteriologic eradication rates of 79% and 88%, respectively; patients treated with meropenem had clinical cure and bacteriologic eradication rates of 86% and 89%, a difference of 7% and 1%, respectively. Patients infected with *B. uniformis* and treated with doripenem had clinical cure and bacteriologic eradication rates of 86% while patients treated with meropenem had clinical cure and bacteriologic eradication rates of 83%, a difference of 3%. Patients infected with *B. vulgatus* and treated with doripenem

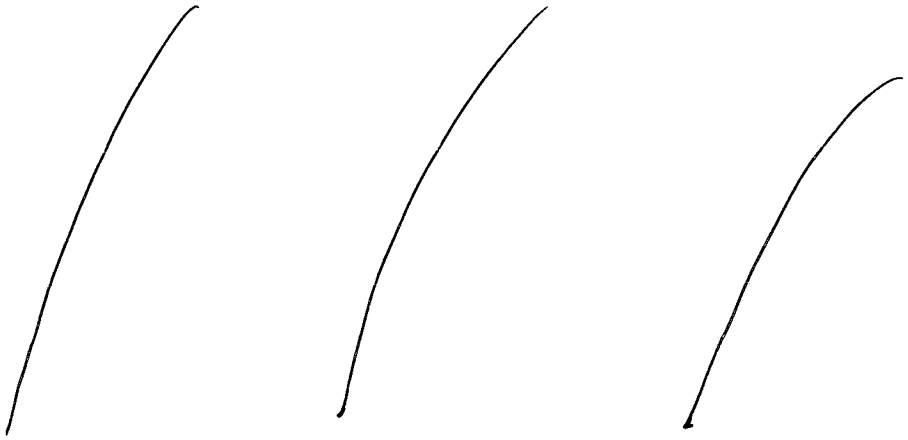
had clinical cure and bacteriologic eradication rates of 100%; patients treated with meropenem had clinical cure and bacteriologic eradication rates of 75%, a difference of 25%. Patients infected with *P. micros* and treated with doripenem had clinical cure and bacteriologic eradication rates of 69% and 85%, respectively, while patients treated with meropenem had clinical cure and bacteriologic eradication rates of 79%, representing differences of 10% for clinical cure and 6% for bacteriologic eradication rates. However, patients infected with *P. micros* and treated with doripenem had a lower clinical cure rate than patients infected with this pathogen and treated with meropenem. **Consequently, this Reviewer recommends the Applicant be granted claims for *B. caccae, B. fragilis, B. thetaiotaomicron, B. uniformis, B. vulgatus* and *P. microns*.**

Gram-negative bacteria

The Applicant seeks label claims for three Gram-negative pathogens including *E. coli, K. pneumoniae* and *P. aeruginosa*. Compared to meropenem treated patients, doripenem treated patients had higher clinical cure and bacteriologic eradication rates for patients infected with either *E. coli* or *P. aeruginosa*. Patients infected with *E. coli* and treated with doripenem had clinical cure and bacteriologic eradication rates of 87% and 88%, respectively, while patients treated with meropenem had clinical cure and bacteriologic eradication rates of 84%, a difference of 4%. Patients infected with *K. pneumoniae* and treated with doripenem had lower clinical cure and bacteriologic eradication rates than patients treated with meropenem. Patients infected with *K. pneumoniae* and treated with doripenem had clinical cure and bacteriologic eradication rates of 72% and 78%, respectively, while patients treated with meropenem had clinical cure and bacteriologic eradication rates of 95% representing differences of 23% for clinical cure and 18% for bacteriologic eradication. Patients infected with *P. aeruginosa* and treated with doripenem had clinical cure and bacteriologic eradication rates of 83% and 85%, respectively, while patients treated with meropenem had clinical cure and bacteriologic eradication rates of 78% and 75%, respectively; these represent differences of 5% for clinical cure and 10% for bacteriologic eradication rates. **Consequently, this Reviewer recommends the Applicant be granted claims for *E. coli, K. pneumoniae* and *P. aeruginosa*.**

Gram-positive bacteria

The Applicant seeks label claims for three Gram-positive pathogens including [redacted] *S. constellatus* and *S. intermedius*. Compared to meropenem treated patients, doripenem treated patients had higher clinical cure and bacteriologic eradication rates for patients infected with [redacted] *S. intermedius*. Patients infected with *S. intermedius* and treated with doripenem had clinical cure and bacteriologic eradication rates of 81% and 83%, respectively, while patients treated with meropenem had clinical cure and bacteriologic eradication rates of 69% and 72%, respectively; these represent differences of 12% for clinical cure and 11% for bacteriologic eradication rates. **Consequently, this Reviewer recommends the Applicant be granted claims for *S. constellatus* or *S. intermedius*.**



The Applicant presents the results of clinical cure and bacteriologic eradications rates for patients infected with different anaerobes stratified by different doripenem MICs in Table 44.

Table 44. Per Pathogen Clinical and Bacteriologic Outcome at TOC by Baseline MIC Level for Anaerobic Pathogens (cIAI)

Organism/Baseline MIC (µg/ml)	N	Clinical Cure (%)	Bacterial Eradication (%)
Anaerobes			
Bacteroides caccae	25	22/25 (88)	23/25 (92)
0.12		3/3 (100)	3/3 (100)
0.25		16/18 (89)	17/18 (94)
0.5		1/1 (100)	1/1 (100)
1		1/2 (50)	1/2 (50)
2		1/1 (100)	1/1 (100)
Bacteroides fragilis	63	54/63 (86)	54/63 (86)
0.12		11/13 (85)	11/13 (85)
0.25		36/43 (84)	36/43 (84)
0.5		4/4 (100)	4/4 (100)
1		2/2 (100)	2/2 (100)
4		1/1 (100)	1/1 (100)
Bacteroides thetaiotaomicron	32	25/32 (78)	28/32 (88)
0.12		3/3 (100)	3/3 (100)
0.25		17/23 (74)	20/23 (87)
0.5		3/4 (75)	3/4 (75)
1		2/2 (100)	2/2 (100)
Bacteroides uniformis	21	18/21 (86)	18/21 (86)
0.12		3/3 (100)	3/3 (100)
0.25		10/12 (83)	10/12 (83)
0.5		4/5 (80)	4/5 (80)
1		1/1 (100)	1/1 (100)

Bacteroides vulgatus	10	10/10 (100)	10/10 (100)
0.12		5/5 (100)	5/5 (100)
0.25		5/5 (100)	5/5 (100)
Peptostreptococcus micros	13	9/13 (69)	11/13 (85)
≤ 0.03		2/5 (40)	3/5 (60)
0.06		4/5 (80)	5/5 (100)
0.12		1/1 (100)	1/1 (100)
0.25		2/2 (100)	2/2 (100)

Source: Tables TEFF102, 103, 105 and 106, Response to Microbiology questions, this submission.

The Applicant presents data from cIAI studies showing the clinical and microbiologic outcomes at each MIC for anaerobic organisms including: *B. caccae, B. fragilis, B. thetaiotaomicron, B. uniformis, B. vulgatus* and *P. micros*. Almost 90% (22/25) of the *B. caccae* isolates had a MIC of ≤ 0.5 µg/ml. Among *B. fragilis* isolates, 89% (56/63) had a MIC value of ≤ 0.25 µg/ml. Almost 94% of *B. thetaiotaomicron* isolates (30/32) had MICs ≤ 0.5 µg/ml. Among *B. uniformis* isolates, 95% (20/21) had MICs ≤ 0.5 µg/ml. Among *B. vulgatus* isolates, 100% (20/20) had MICs ≤ 0.25 µg/ml. Finally, all *P. micros* isolates had MICs of ≤ 0.25 µg/ml. Among *B. fragilis* and *B. uniformis* isolates, the two species deemed adequate for inclusion in the label claims, 85% (71/84) of isolates had a MIC value of ≤ 0.25 µg/ml. In the case of both organisms, this MIC value was also the mode. Overall, there was little correlation of MIC with clinical or bacteriologic outcome.

The Applicant presents the results of clinical cure and bacteriologic eradications rates for patients infected with different Gram-negative aerobes stratified by different doripenem MICs in Table 45.

Table 45. Per Pathogen Clinical and Bacteriologic Outcome at TOC by Baseline MIC Level for Gram-negative Pathogens (cIAI)

Organism/Baseline MIC (µg/ml)	N	Clinical Cure (%)	Bacterial Eradication (%)
Gram-negative aerobes			
Eschenchia coli	207	180/207 (89)	182//207 (88)
≤ 0.03		166/190 (87)	168/190 (88)
0.06		14/16 (88)	14/16 (88)
0.12		0/1 (0)	0/1 (0)
Klebsiella pneumoniae	30	22/30 (73)	24/30 (80)
≤ 0.03		9/11 (82)	9/11 (82)
0.06		12/18 (67)	14/18 (78)
0.12		1/1 (100)	1/1 (100)
Pseudomonas aeruginosa	38	32/38 (84)	33/38 (89)
≤ 0.03		1/1 (100)	1/1 (100)
0.06		6/7 (86)	7/7 (100)
0.12		4/5 (80)	4/5 (80)
0.25		8/8 (100)	8/8 (100)
0.5		7/8 (88)	7/8 (88)

1	4/7 (57)	4/7 (57)
2	2/2 (100)	2/2 (100)

Source: Tables TEFF102, 103, 105 and 106, Response to Microbiology questions, this submission.

The Applicant presents data from cIAI studies showing the clinical and microbiologic outcomes at each MIC for Gram-negative aerobic organisms including: *E. coli, K. pneumoniae* and *P. aeruginosa.* More than 99% (206/207) of the *E. coli* isolates had a MIC of ≤ 0.06 µg/ml. All of these isolates had a MIC value of ≤ 0.12 µg/ml and the MIC mode was ≤ 0.03 µg/ml. Among *K. pneumoniae* isolates, 97% (29/30) had a MIC value of ≤ 0.06 µg/ml which was also the MIC mode. All of these isolates had a MIC value of ≤ 0.12 µg/ml. Among *P. aeruginosa* isolates, 95% (36/38) had MICs ≤ 1 µg/ml. Only 34% (13/38) of isolates has a MIC of ≤ 0.12 µg/ml. Among *E. coli* and *P. aeruginosa* isolates, the two species deemed adequate for inclusion in the label claims, MIC values were quite different between the two organisms. While the mode MIC among *E. coli* isolates was ≤ 0.03 µg/ml, MICs among *P. aeruginosa* isolates were relatively evenly distributed. Overall, there was little correlation of MIC with clinical or bacteriologic outcome.

The Applicant presents the results of clinical cure and bacteriologic eradications rates for patients infected with different Gram-positive aerobes stratified by different doripenem MICs in Table 46.

Table 46. Per Pathogen Clinical and Bacteriologic Outcome at TOC by Baseline MIC Level for Gram-positive Pathogens (cIAI)

Organism/Baseline MIC (µg/ml)	N	Clinical Cure (%)	Bacterial Eradication (%)
Gram-positive aerobes			
Enterococcus faecalis	18	13/18 (72)	14/18 (78)
2		6/8 (75)	7/8 (88)
4		6/8 (75)	6/8 (75)
8		1/2 (50)	1/2 (50)
Streptococcus constellatus	10	9/10 (90)	9/10 (90)
≤ 0.03		5/6 (83)	5/6 (83)
0.06		3/3 (100)	3/3 (100)
0.12		1/1 (100)	1/1 (100)
Streptococcus intermedius	36	29/36 (81)	30/36 (83)
≤ 0.03		27/34 (79)	28/34 (82)
0.06		2/2 (100)	0
0.12		0	2/2 (100)

The Applicant presents data from cIAI studies showing the clinical and microbiologic outcomes at each MIC for Gram-positive aerobic organisms including: *E. faecalis, S. constellatus* and *S. intermedius.* About 90% (16/18) of the *E. faecalis* isolates had a MIC of ≤ 4 µg/ml. Most isolates had a MIC value of either 2 or 4 µg/ml there was no MIC mode. Among *S. constellatus* isolates, 90% (9/10) had a MIC value of ≤ 0.06 µg/ml

while the MIC mode was ≤ 0.03 µg/ml. All of these isolates had a MIC value of ≤ 0.12 µg/ml. Among *S. intermedius* isolates, 94% (34/36) had MICs ≤ 0.03 µg/ml. Among *E. faecalis* and *S. intermedius* isolates, the two species deemed adequate for inclusion in the label claims, MIC values were quite different between the two organisms. While the majority MICs among *E. faecalis* isolates was ≤ 4 µg/ml and evenly distributed, the MIC mode for *S. intermedius* isolates was much lower (≤ 0.03 µg/ml). Again, there was little correlation of MIC with clinical or bacteriologic outcome.

DEVELOPMENT OF RESISTANCE IN CLINICAL ISOLATES

Pairs of clinical isolates that exhibited ≥ 2 step increases in doripenem MICs during doripenem treatment in the cUTI and IAI trials were examined for potential resistance development. Isolate pairs from nine patients were identified from the doripenem arm of the DOR05, DOR06, and DOR08 trials. No patient from the DOR07 trial had a pair of isolates that filled these criteria. Table 47 lists the set of isolates received from the central microbiology laboratory that were examined in these studies.

In order to determine if the pre- and post-treatment isolates were the same or were unrelated pathogens, pulsed-field gel electrophoresis (PFGE) was performed on all of the isolate pairs. The DNA restriction patterns were interpreted according to the guidelines of Tenover et al., where one to three band differences are considered related, four to six differences are considered possibly related, and seven or more band differences between isolates are considered unrelated. Isolates were designated identical if there were no visible band differences on the PFGE gel.

Table 47. Development of Doripenem Resistance on Therapy in Clinical Isolates from DOR05, DOR06, and DOR08

Subject ID	Visit	Pathogen	Study	MIC (µg/ml) Central Laboratory	MIC (µg/ml) Applicant	Step Increase	PFGE Results
20107094	SCR	*E. coli*	DOR05	≤ 0.015	ND	2	Different
	TOC			0.06			
20507208	SCR	*S. marcescens*	DOR05	0.12	ND	2	Different
	TOC			0.5			
	LFU			0.25			
35000079	SCR	*P. aeruginosa*	DOR06	8	4	2	Identical
	TOC			32	16		
45500152	SCR	*E. faecalis*	DOR06	0.12	2	4	Identical
	LFU			2	8		
45500330	SCR	*E. cloacae*	DOR06	≤ 0.015	0.06	4	Possibly
	TOC			0.25	0.5		Related
45500372	SCR	*E. cloacae*	DOR06	0.03	ND	5	Different
	LFU			1			
45500391	SCR	*K. pneumoniae*	DOR06	0.03	ND	2	NA, *
	LFU			0.12			NA, **
45500405	SCR	*E. coli*	DOR06	≤ 0.015	0.12	2	Identical

	TOC			0.06	0.06		
5402058	SCR	*P. aeruginosa*	DOR08	1	1	3	Identical
	EFU			8	16		

SCR, Screening; TOC, Test of Cure; LFU, Late Follow Up; EFU, Early Follow Up.
*reidentified as *E. cloacae*; ** confirmed as *K. penumoniae*
Note: these MIC susceptibility values were determined at the Central Laboratory.
Source: Tables 20—22, this submission.

From the PFGE results, five of the nine pairs that were identical or possibly-related were evaluated further. The isolate pairs that were different were determined to represent re-infection with a different isolate and were not considered further in this study.

The purpose of this study was to identify molecular changes that occurred during doripenem treatment that resulted in a two step or more increase in doripenem MIC values between screening and post-treatment samples. Isolate pairs from nine patients included four pairs that were identical or possibly-related isolates. These consisted of one possibly-related pair of *E. cloacae*, one identical pair of *E. faecalis*, and two identical pairs of *P. aeruginosa*.

The possibly-related *E. cloacae* pair had a potential increase in AmpC ß-lactamase expression coupled with an additional acquired SHV ß-lactamase. Because the PFGE profiles differed slightly, it was not possible to confirm that the same isolate was present during the course of the doripenem treatment. However, the post-treatment cell extract produced 6.5-fold more nitrocefin hydrolyzing activity. The doripenem MIC values of the screening and post-treatment isolates, determined by the Central Laboratory were 0.015 µg/ml and 0.25 µg/ml, respectively. This represents a four dilution step increase.

The *E. faecalis* pair, with pre- and post-treatment doripenem MIC values of 0.12 µg/ml and 2 µg/ml (as determined by the Central Laboratory), respectively, represents a four step increase. These isolates did not have a ß-lactamase-associated increase in MIC, as would be expected for the enterococci.

One *P. aeruginosa* pair demonstrated pre- and post-treatment doripenem MIC values of 8 µg/ml and 32 µg/ml, respectively, representing a two dilution step increase. The other *P. aeruginosa* pair demonstrated pre- and post-treatment doripenem MIC values of 1 µg/ml and 8 µg/ml, respectively representing a three dilution step increase.

The two *P. aeruginosa* pairs were negative by PCR for ß-lactamases of the VIM, SPM, IMP, OXA and CTX-M classes. One pair of isolates demonstrated a modest increase (3-fold) in ß- lactamase activity compared to the baseline isolate. Evaluation of gene expression by RT-PCR revealed that gene expression changes consistent between these isolate pairs included the decreased expression of *oprD*, *oprN*, *oprJ* and *mexD*, genes that may be associated with decreased intracellular concentrations of carbapenems. A larger number of clinical *P. aeruginosa* isolates will need to be characterized in order to draw

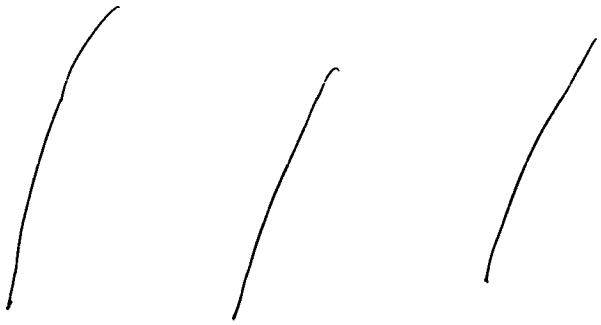
firm conclusions regarding the effects of *oprD*, *ampC* and efflux gene expression levels to the MIC.

Reviewer's comments: The Applicant conducted a study to elucidate the mechanisms of resistance among pairs of clinical isolates that demonstrated at least a two step increase in doripenem MICs between baseline and on therapy treatment. There were nine pairs of isolates from the doripenem arm of the clinical trials where doripenem MIC values increased at least two steps over the course of treatment. When these pairs were tested for known carbapenem resistance mechanisms, no mechanism was identified for the *E. faecalis* pair. The *E. cloacae* isolates were not confirmed to be of the same parentage; however, additional ß-lactamases, and higher ß-lactamase hydrolytic activity, were shown to be present in the more resistant isolate. The two *P. aeruginosa* pairs exhibited some changes in efflux and porin genes, in addition to changes in ß-lactamase activity.

The Applicant is conducting additional studies to define these mechanisms more precisely. As these increases in doripenem susceptibility on therapy are troublesome, ***this Reviewer recommends the Applicant conduct a Phase IV study to examine occurrence of doripenem resistance during therapy***. This study should consist of two parts. First, specimens should be collected at baseline and at test of cure for the purpose of determining doripenem MIC susceptibilities of these isolates at these time points. Second, mechanisms of resistance should be determined for isolates that have demonstrated a two step increase or more in doripenem MIC values.

BREAKPOINT DISCUSSIONS

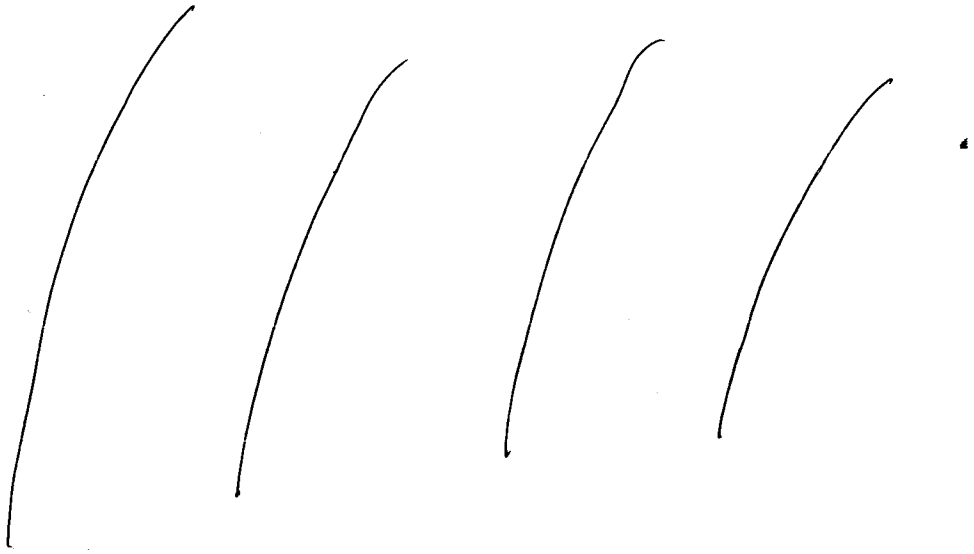
Applicant Proposed Interpretive Criteria



The Applicant asserts that the data suggest one set of breakpoints can be used to categorize organisms from both clinical indications, as no differences were seen in clinical cure rates across the two indications over a range of doripenem MICs. Differing sets of breakpoints by indication may be warranted in special circumstances, e.g. for infections with markedly different pharmacokinetic/pharmacodynamic values (e.g. meningitis). However, regarding the indications in this application, the cUTI indication

includes pyelonephritis (often with concurrent bacteremia) and appropriate systemic drug concentrations (and PK/PD values) would need to be similar to those for cIAI. Furthermore, if different breakpoints were applied to multiple indications, the resultant complex schema could lead to confusion. Laboratories often receive cultures without identification of the specimen source, and would not know which indication-specific breakpoints to apply. In addition, if the same organism were isolated from two different sites, different interpretations of the same MICs could be reported, leading to confusion. The Applicant proposes the following MIC breakpoints:

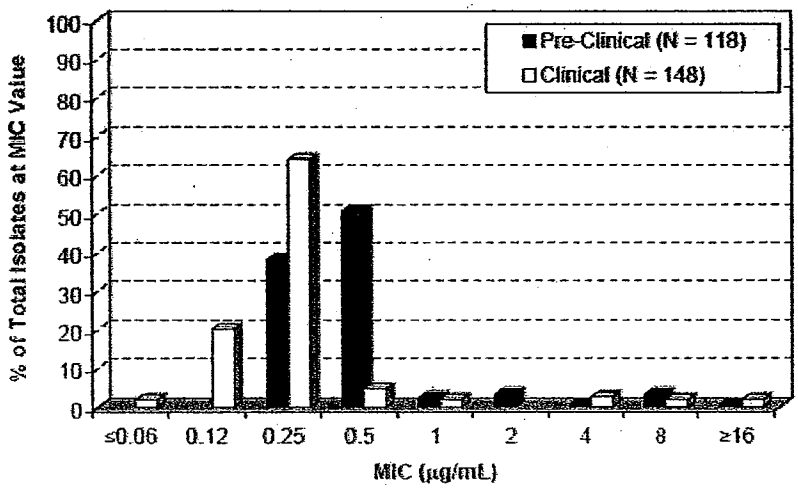
Table 48. Applicant Proposed MIC and Disk Diffusion Interpretive Criteria for Doripenem



Reviewer Proposed Interpretive Criteria
Anaerobes (cIAI only)
In Vitro Isolates. The Applicant presents MIC90 data from 164, 44 and 39 isolates (3 studies) of *B. fragilis, B. thetaiotaomicron* and *other Bacteroides spp.*, respectively. MIC90s ranged from 0.5 to 2 µg/ml. No data are presented for *P. microns*, *B. caccae* or *B. uniformis*.
Monte Carlo Simulations. Target attainment values for all anaerobes causing cIAI were 97.8, 97.3 and 96.9% at T > MIC values of 25%, 30% and 35%, respectively.
Clinical Isolates. Among *B. fragilis* and *B. uniformis* isolates, 85% (71/84) of isolates had a MIC value of ≤ 0.25 µg/ml. In the case of both organisms, this MIC value was also the mode. Among *B. fragilis* isolates, 89% (56/63) had a MIC value of ≤ 0.25 µg/ml. Among *B. caccae* isolates, 84% (21/25) had a MIC ≤ 0.25 µg/ml. Among *B.*

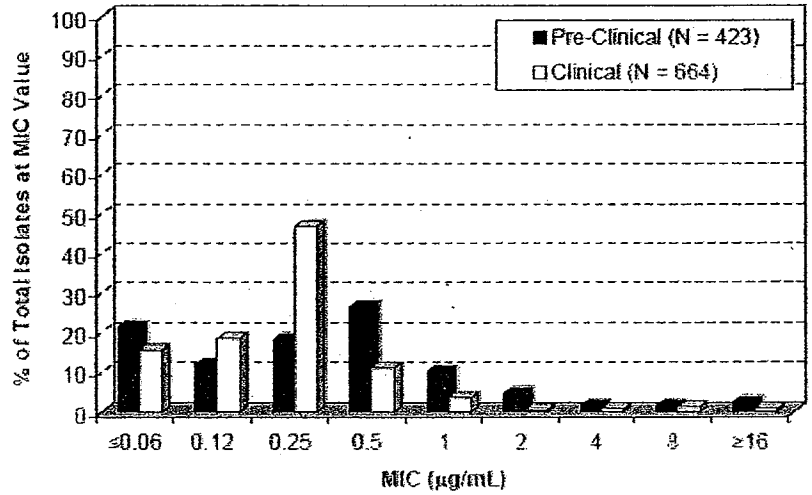
thetaiotaomicron isolates, 26/32 (81%) had a MIC ≤ 0.25 µg/ml. All *B. vulgatus* isolates (10/10) had a MIC ≤ 0.25 µg/ml.

Figure 7: Frequency Distribution of Doripenem MIC against *Bacteroides fragilis*. From Preclinical and Complicated Intraabdominal Infection Studies



Source: Figure 4.2.2.17, this submission.

Figure 8: Frequency Distribution of Doripenem MIC against Anaerobes from Preclinical and Complicated Intraabdominal Infection Studies



Source: Figure 4.2.2.14, this submission.

Enterobacteriaceae

In Vitro Isolates. The Applicant presents susceptibility data from over a thousand isolates from several studies. MIC90s ranged from < 0.015 to 2 µg/ml.

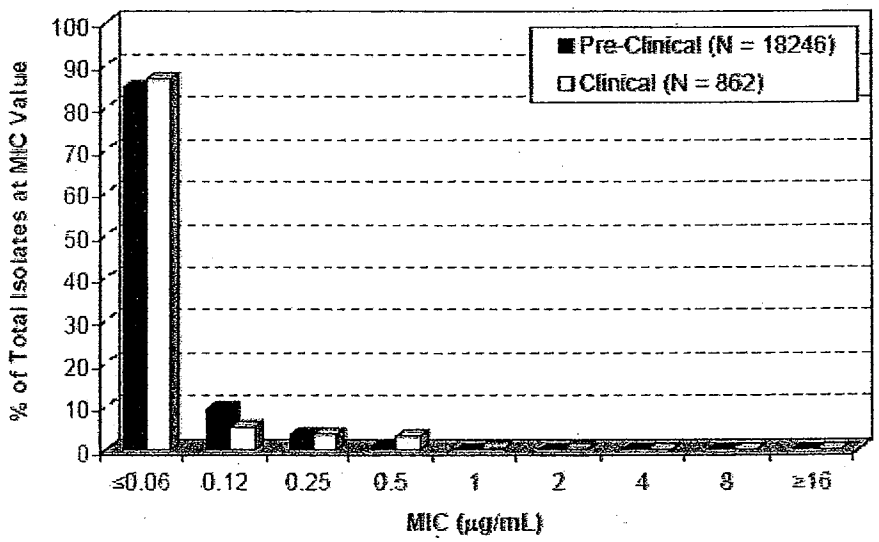
Animal Efficacy Data. In a mouse peritonitis model, two different *E. coli* isolates with MICs = 0.03 µg/ml displayed ED50s of 0.04 mg/kg/dose (*E. coli* EC14) and 1.42 mg/kg/dose (*E. coli* C-11).

Monte Carlo Simulations. Target attainment values for *Enterobacteriaceae* causing cIAI were 100, 100 and 99.9% at T > MIC values of 25%, 30% and 35%, respectively. Target attainment values for *Enterobacteriaceae* causing cUTI were 99.8, 99.7 and 99.6% at T > MIC values of 25%, 30% and 35%, respectively.

Clinical Isolates.

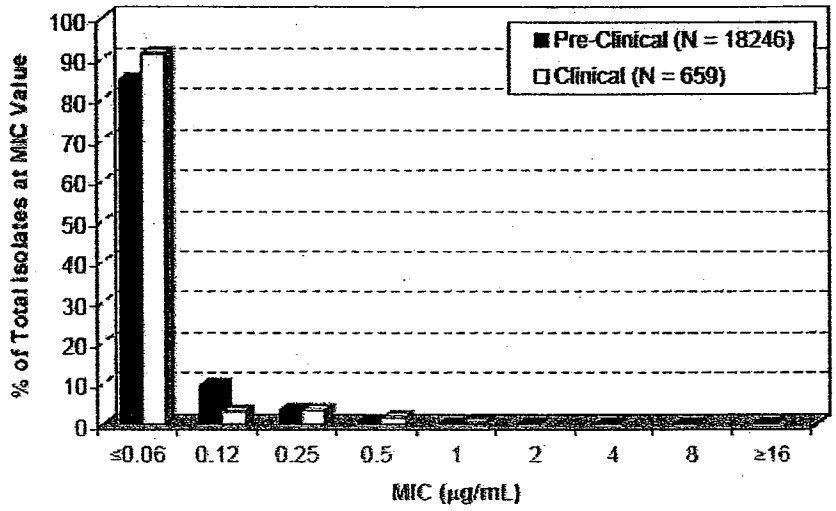
- **cIAI**: More than 80% of preclinical and 90% of clinical isolates of *Enterobacteriaceae* had a MIC of ≤ 0.06 µg/ml. All of these isolates had a MIC value of ≤ 0.12 µg/ml and the MIC mode was ≤ 0.03 µg/ml.
- **cUTI:** Among *E. coli* isolates, 90% (301/335) had a MIC value of ≤ 0.03 µg/ml which was also the MIC mode. All of these isolates had a MIC value of ≤ 0.12 µg/ml.

Figure 9: Frequency Distribution of Doripenem MICs *Enterobacteriaceae* Isolates from cUTI and Surveillance



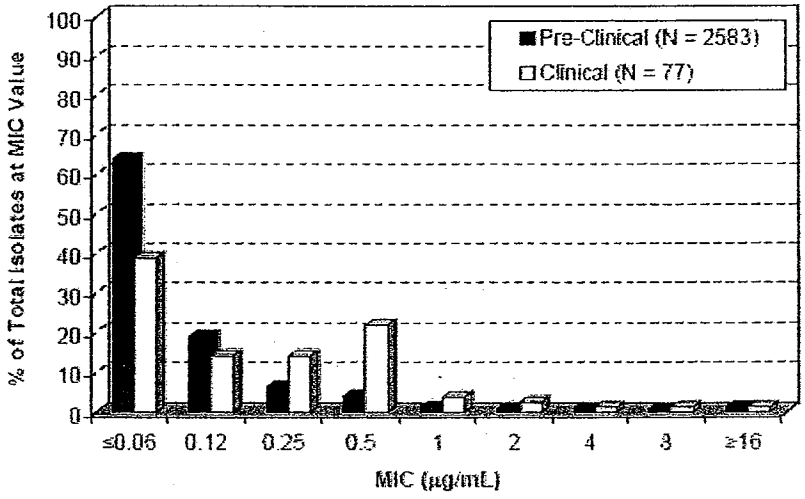
Source: Figure 4.2.1.1, NDA 22-106 SN001 submission.

Figure 10: Frequency Distribution of Doripenem MICs from *Enterobacteriaceae* Isolates from cIAI and Surveillance



Source: Figure 4.2.2.1, NDA 22-106 SN001 submission.

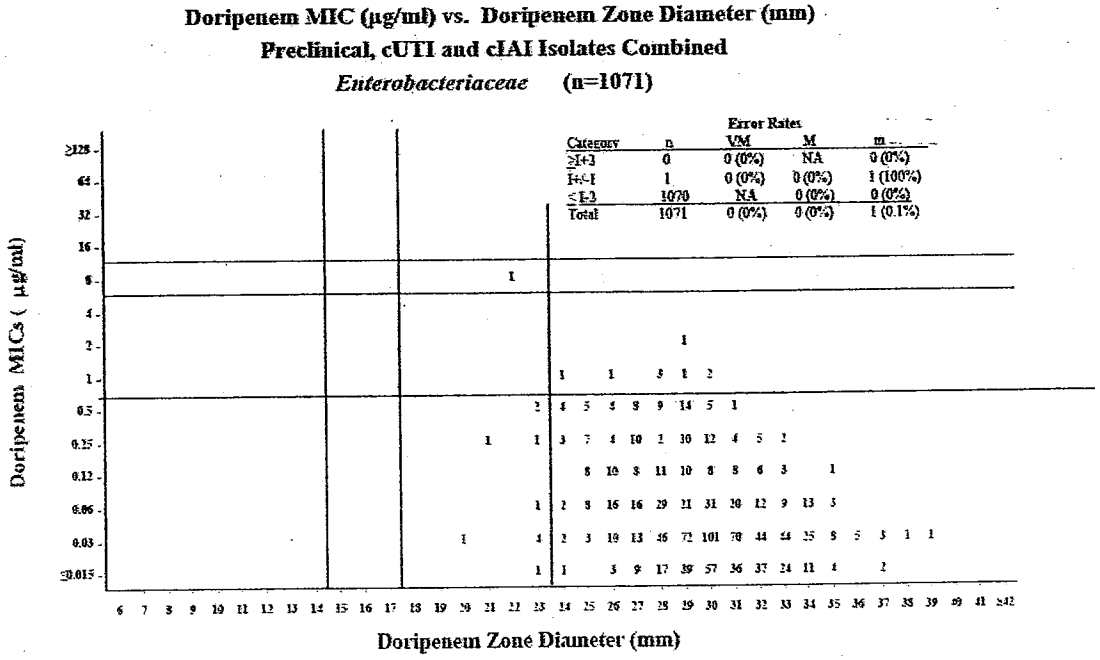
Figure 11: Frequency Distribution of Doripenem MIC against ESBL *Enterobacteriaceae* from Preclinical and Complicated Urinary Tract Infection Studies



Source: Figure 4.2.1.2, 04 June 2007 submission.

Correlation of MIC Interpretive Criteria with Zone Size Diameters. Four scattergrams of preclinical isolates only, cUTI isolates only, cIAI isolates only and preclinical, cUTI and cIAI isolates combined were supplied by the Applicant and examined. Below is the scattergram for the preclinical, cUTI and cIAI isolates combined. Scattergrams for the preclinical, cUTI and cIAI isolates were similar to this scattergram containing the combined data (Figure 12).

Figure 12. Scattergram of Preclinical, cUTI and cIAI *Enterobacteriaceae* Isolates Combined.



Source: Figure 6.6, NDA 22-106, SN001.

NOTE: Error rates in diagram are not the error rates for the Agenc's proposed interpretive criteria. See following text for these error rates.

Here the red lines represent the breakpoints proposed by this Reviewer. Breakpoints of "susceptible" for MIC and zone diameters are ≤ 0.5 mg/ml and ≥ 23 mm, respectively. Due to the lack of "resistant" isolates, "intermediate" and "resistant" categories cannot be assigned. Using these breakpoints, 99% of isolates are "susceptible" by MIC and zone diameter. Using CLSI guidelines for acceptable discrepancy rates, only 9 (0.8%) isolates have a very major discrepancy rate while 12 (1.1%) isolates have a major discrepancy rate, both acceptable values.

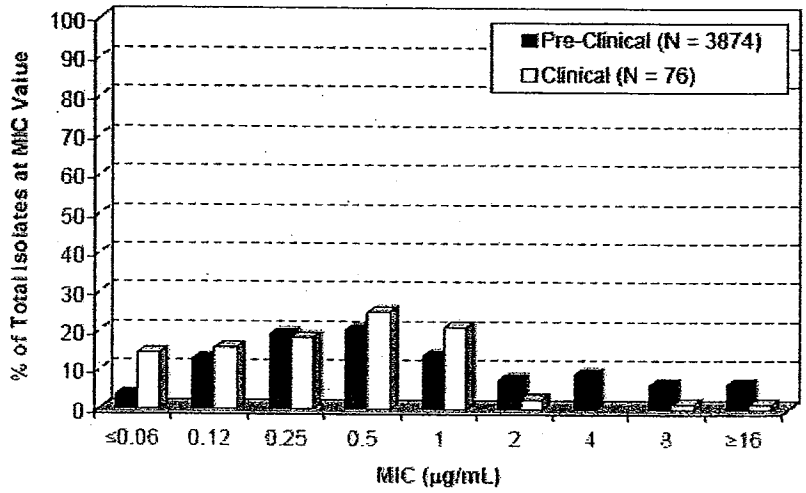
***P. aeruginosa* (cIAI only)**

In Vitro Isolates. MIC90 data from isolates with unknown or known antibiotic resistance totaled 1105 isolates from 17 studies. These MIC90s ranged from 0.5 to 64 µg/ml. However, among isolates of unknown (if any) antibiotic resistance (5 studies, 337 isolates) the MIC90s ranged from 0.5 to 12.5 µg/ml.

Animal Efficacy Data. In a mouse peritonitis model, seven different isolates ranging from MICs of 0.25 to 8 µg/ml displayed ED50s ranging from 0.17 mg/kg/dose (*P. aeruginosa* SR10411) to 31.2 mg/kg/dose (*P. aeruginosa* TUH302, ceftazidime resistant).

Monte Carlo Simulations. Target attainment values for non-*Enterobacteriaceae* causing cIAI were 98.1, 97.6 and 96.7% at T>MIC values of 25%, 30% and 35%, respectively. Target attainment values for non-*Enterobacteriaceae* causing cUTI were 83.6, 80.7 and 77.7% at T > MIC values of 25%, 30% and 35%, respectively.
Clinical Isolates. Among *P. aeruginosa* isolates from patients treated for cIAI, 95% (36/38) had MICs ≤ 1 µg/ml.

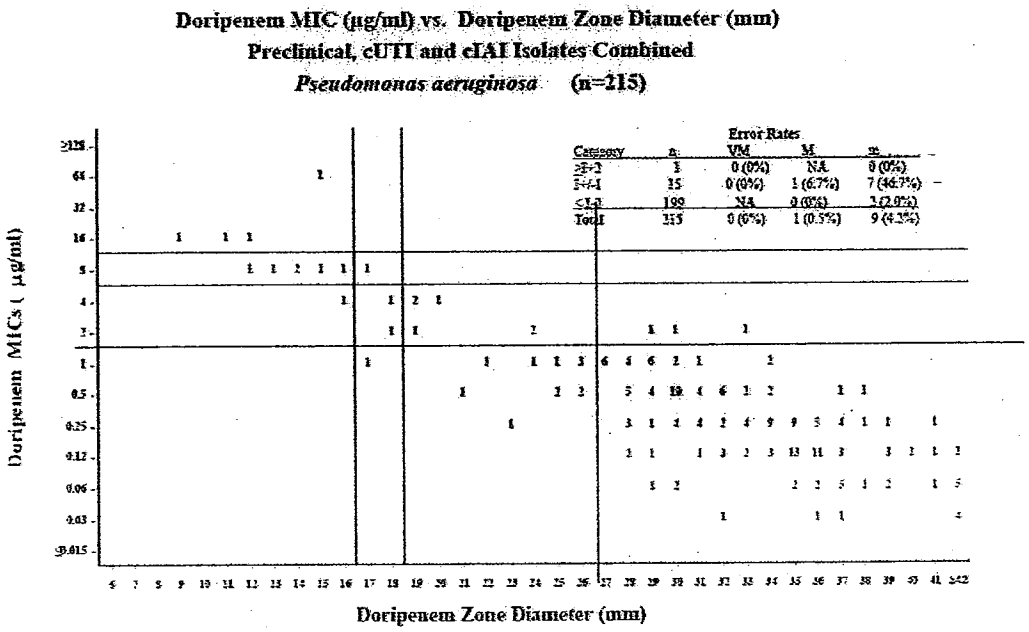
Figure 13: Frequency Distribution of Doripenem MIC against *Pseudomonas aeruginosa* From Preclinical and Complicated Intraabdominal Infection Studies



Source: Figure 4.2.2.5, this submission.

Correlation of MIC Interpretive Criteria with Zone Size Diameters. Four scattergrams of preclinical isolates only, cUTI isolates only, cIAI isolates only and preclinical, cUTI and cIAI isolates combined were supplied by the Applicant and examined. Below is the scattergram for the preclinical, cUTI and cIAI isolates combined. Scattergrams for the preclinical, cUTI and cIAI isolates were similar to this scattergram containing the combined data.

Figure 14. Scattergram of Preclinical, cUTI and cIAI *P. aeruginosa* Isolates Combined.



Source: Figure 6.72, NDA 22-106, SN001.
NOTE: Error rates in diagram are not the error rates for the Agenc's proposed interpretive criteria. See following text for these error rates.

Best Possible Copy

Breakpoints of "susceptible" for MIC and zone diameters are ι, respectively. Due to the lack of "resistant" isolates, "intermediate" and "resistant" categories cannot be assigned. Using these breakpoints, 89% and 90% of isolates are "susceptible" by MIC and zone diameter, respectively. Using CLSI guidelines for acceptable discrepancy rates, only 3 isolates (1.5%) have a very major discrepancy rate while 5 isolates (2.5%) have a major discrepancy rate, both acceptable values.

***A. baumannii* (cUTI only)**

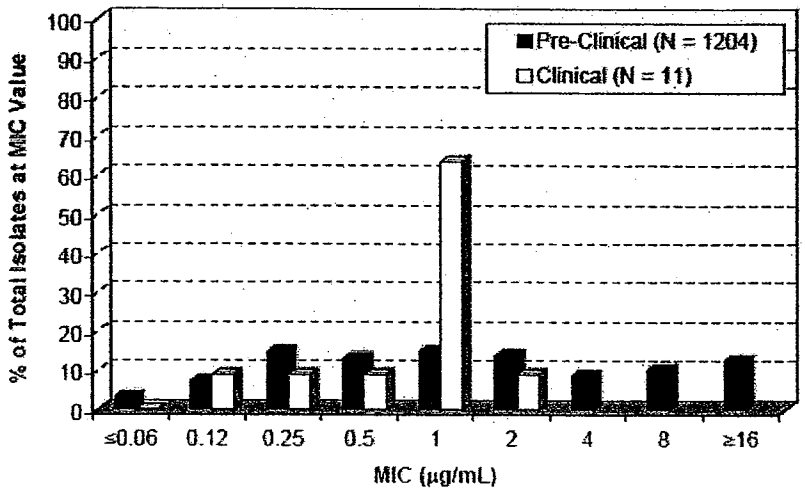
In Vitro Isolates. MIC90 data from isolates with known or unknown antibiotic resistance totaled 73 isolates from 3 studies. These MIC90s ranged from 1 to > 16 µg/ml.

Animal Efficacy Data. No data available.

Monte Carlo Simulations. Target attainment values for non-*Enterobacteriaceae* causing cIAI were 98.1, 97.6 and 96.7% at T > MIC values of 25%, 30% and 35%, respectively. Target attainment values for non-*Enterobacteriaceae* causing cUTI were 83.6, 80.7 and 77.7% at T > MIC values of 25%, 30% and 35%, respectively.

Clinical Isolates. Among *A. baumannii* isolates from patients treated for cUTI, 90% (9/10) had MICs ≤ 1 µg/ml.

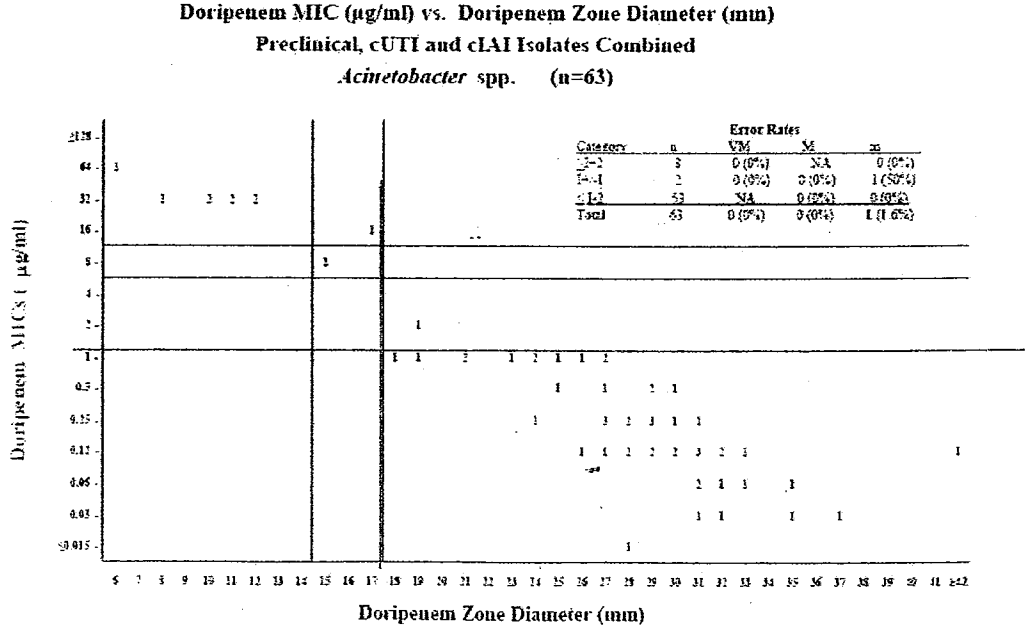
Figure 15: Frequency Distribution of Doripenem MIC Against *Acinetobacter* spp. From Preclinical and Complicated Urinary Tract Infection Studies



Source: Figure 4.2.1.16, this submission.

Correlation of MIC Interpretive Criteria with Zone Size Diameters. Four scattergrams of preclinical isolates only, cUTI isolates only, cIAI isolates only and preclinical, cUTI and cIAI isolates combined were supplied by the Applicant and examined. Below is the scattergram for the preclinical, cUTI and cIAI isolates combined. Scattergrams for the preclinical, cUTI and cIAI isolates were similar to this scattergram containing the combined data.

Figure 16. Doripenem MIC (µg/ml) vs. Doripenem Zone Diameter (mm) Preclinical, cUTI and cIAI Isolates Combined-*Acinetobacter* spp.

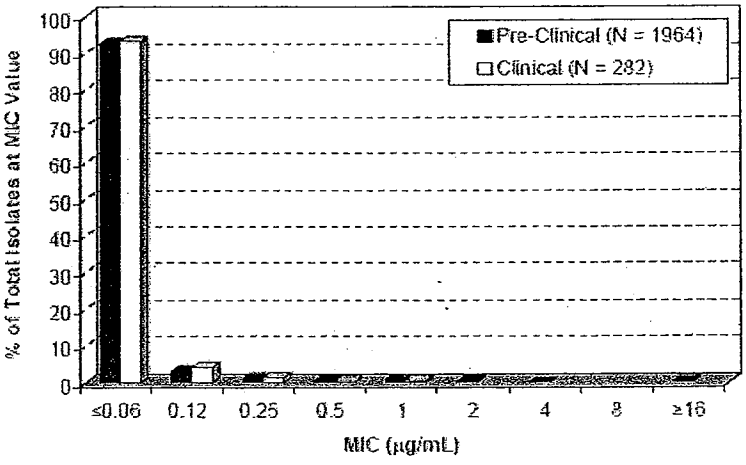


Source: Figure 6.66, NDA 22-106, SN001.
NOTE: Error rates in diagram are not the error rates for the Agenc's proposed interpretive criteria. See following text for these error rates.

Here the red lines represent the breakpoints proposed by this Reviewer. Breakpoints of "susceptible" for MIC and zone diameters are ≤ 1 µg/ml and ≥ 17 mm, respectively. Due to the lack of "resistant" isolates, "intermediate" and "resistant" categories cannot be assigned. Using these breakpoints, 82% and 84% of isolates are "susceptible" by MIC and zone diameter, respectively. Using CLSI guidelines for acceptable discrepancy rates, no isolates (0%) have a very major discrepancy rate or a major discrepancy rate, both acceptable values.

***S. intermedius* and *S. constellatus* (cIAI only)**
In Vitro Isolates. The Applicant did not present these susceptibility data.
Monte Carlo Simulations. Target attainment values for *Streptococcus* spp. (not *S. pneumoniae*) causing cIAI were 100, 99.99 and 99.99% at T>MIC values of 25%, 30% and 35%, respectively.
Clinical Isolates. Among *S. intermedius* isolates, 94% (34/36) had MICs ≤ 0.03 µg/ml. While the majority MICs among *E. faecalis* isolates was ≤ 4 µg/ml and evenly distributed, the MIC mode for *S. intermedius* isolates was much lower (≤ 0.03 µg/ml).

Figure 15: Frequency Distribution of Doripenem MIC against *Streptococcus* spp. Other than *S. pneumoniae* from Preclinical and Complicated Intraabdominal Infection Studies



Source: Figure 4.2.2.13, this submission.

Reviewer's comments: MIC and disk diffusion interpretive criteria were determined using susceptibility data of *in vitro* isolates, animal efficacy data, pharmacodynamic data and susceptibility data of *in vivo* isolates and correlation of MIC and disk diffusion data [7].

Division of Anti-Infective and Ophthalmology Products

The Applicant supplied correlation of MIC and disk diffusion data in the form of scattergrams for *E. coli* and *P. aeruginosa*. However, the Applicant does not provide any scattergrams of anaerobic species, specifically *B. fragilis* and *B. uniformis*. Consequently, disk diffusion interpretive criteria could not be assigned to these organisms. The Applicant supplies a scattergram for *Streptococci* other than *Streptococcus pneumoniae* but not the individual species. Consequently, disk diffusion interpretive criteria could not be assigned to these organisms.

This Reviewer recommends the following MIC and disk diffusion interpretive criteria:

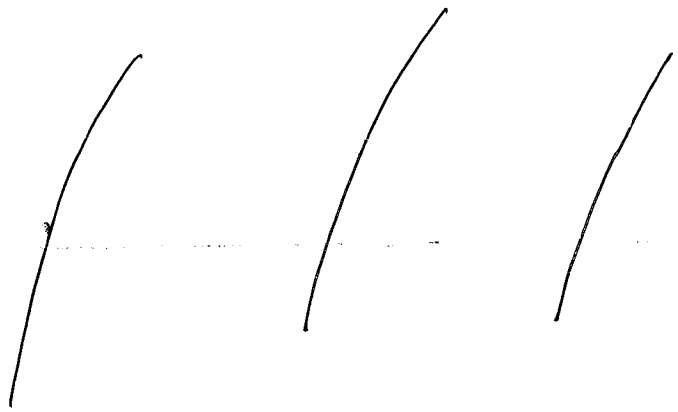
Reviewer Recommended Interpretive Criteria

	MIC (µg/ml)			Zone Diameter (mm)		
	S	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae	≤ 0.5	--	--	≥ 23	--	--
Pseudomonas aeruginosa	≤ —	--	--	≥ 24	--	--
Acinetobacter baumannii	≤ 1	--	--	≥ 17	--	--
Streptococcus anginosus group (*S. intermedius* and *S. constellatus*)	—	--	--	TBD*	--	--
Anaerobes	≤ —	--	--	--	--	--

The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results suggestive of "Nonsusceptible" should be submitted to a reference laboratory for further testing.
*To be determined

Microbiology Section of the Package Insert

Insertions are indicated by blue type and underlined. ~~Deletions are indicated by red type and stricken through~~.

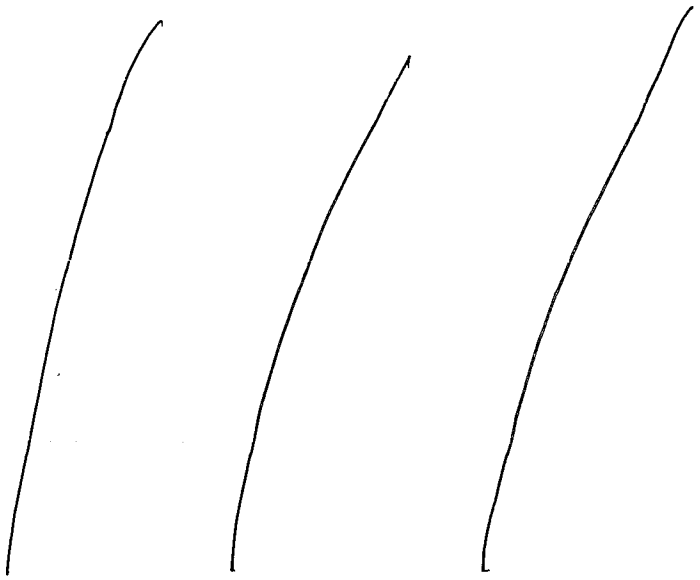


7 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process



17. REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – 7th ed., CLSI document M7-A7, CLSI, 940 West Valley Rd., Suite 1400, Wayne, PA. 19087-1898, 2006.

2. CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard – 9th ed. CLSI document M2-A9, CLSI, Wayne, PA. 19087-1898, 2006.

3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing -17th Informational Supplement. CLSI document M100-S17, CLSI, Wayne, PA. 19087-1898, 2007.

4. CLSI. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – 7th ed., CLSI document M11-A7, CLSI, Wayne, PA 19087-1898, 2007.

Division of Anti-Infective and Ophthalmology Products

NDA 22-106 SN000 | Clinical Microbiology Review #1
Doripenem | Peter Coderre, PhD
Johnson & Johnson | 20 August 2007

REVIEW REFERENCES

1. Levison ME, Bush LM. 2005. Intra-abdominal infection. In: *Principles and Practice of Infectious Diseases*. 6th edition. Eds. Mandell GL, Bennett JE, Dolin R. pp927—51. Elsevier Churchill Livingstone, Philadelphia.

2. Paterson DL, Rossi F, et al. 2005. *In vitro* susceptibilities of aerobic and facultative gram-negative bacilli isolated from subjects with IAI worldwide: the 2003 Study for Monitoring Antimicrobial Resistance Trends (SMART). J Antimicrob Chem 55:965-73.

3. Sobel JD, Kaye D. 2005. Urinary tract infections. In: *Principles and Practice of Infectious Diseases*. 6th edition. Eds. Mandell GL, Bennett JE, Dolin R. pp875—905. Elsevier Churchill Livingstone, Philadelphia.

4. Zhanel, GG, Hisanag, TL, Laing NM, et al. 2006. Antibiotic resistance in *Escherichia coli* out subject urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). Int J Antimicrob Agents 27:468-75.

5. Amsterdam D. 1996. Susceptibility testing of antimicrobials in liquid media. In: *Antibiotics in Laboratory Medicine*. Ed. Lorian V. Lippincott Williams & Wilkins, Philadelphia.

6. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; 15th Informational Supplement. CLSI document M100-S15. Clinical and Laboratory Standards Institute, Wayne, PA, 2005

7. Turnidge J, Paterson DL. 2007. Setting and revising antibacterial susceptibility breakpoints. Clin Microbiol Rev. 20:391-408.

8. Ruoff KL, Whiley RA, Beighton D. 2003. Streptococcus. In: Manual of Clinical Microbiology, 8th edition. Murray PR, ed. in chief. ASM Press, Washington, DC.

Peter Coderre, Ph.D
Microbiology Reviewer

FMarsik, PhD/MicroTL/HFD-520
1 Oct 07 FIN FJM

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

/s/

Peter Coderre
10/1/2007 02:50:33 PM
MICROBIOLOGIST

Frederic Marsik
10/1/2007 03:02:55 PM
MICROBIOLOGIST

Product Quality Microbiology Review

28 September 2007

NDA: 22-106

Drug Product Name
Proprietary: Doripenem for Injection
Non-proprietary: Doripenem Monohydrate
Drug Product Priority Classification: S

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
12 DEC 2006	13 DEC 2006	01 MAR 2007	01 MAR 2007
09 AUG 2007	09 AUG 2007	N/A	N/A

Applicant/Sponsor
Name: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Address: 920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602
Representative: George Marchesini
Telephone: 908-704-5389

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommended for Approval.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original NDA.

2. **SUBMISSION PROVIDES FOR:** A new drug.

3. **MANUFACTURING SITE:**
The — drug substance and the drug product are manufactured at the following site:
Shionogi Kanegasaki Plant
Shionogi & Company, Ltd.
7 Nishinemoriyama, Kanegasaki-cho
Isawa-gun, Iwate-ken, Japan
Drug Establishment Registration Number 3002808135

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Powder for injection in 20 mL glass vial.
- Intravenous injection.
- 500 mg (anhydrous basis)/vial.

5. **METHOD(S) OF STERILIZATION:** —

6. **PHARMACOLOGICAL CATEGORY:** Indicated for the treatment of complicated intra-abdominal infections and complicated urinary tract infections.

B. **SUPPORTING/RELATED DOCUMENTS:** None.

C. **REMARKS:**
The NDA submission is provided in the eCTD format.

There was an Initial Quality Assessment performed by the PAL on 08 JAN 2007. The PAL review noted the following regarding the microbiological product quality of the drug substance:

/ / / / /

In addition, the following comments from the PAL review relates to the microbiological quality of the drug product:

3. **Is the container-closure integrity testing procedure adequate for sterility assurance?**
4. **There are no preservatives in the DP. The reconstituted product though shown to be stable for — hours, may not necessarily remain sterile.**

Each of the areas identified (above) by the PAL will be considered in this review.

On 28 June 2007, this reviewer forwarded the following questions and comments to the OND Project Manager for communication with the applicant:

- Provide validation of the ability of
- The following statement is found in Section 2.3 of Module 3.2.P.3.5 concerning

The applicant amended the NDA on 09 August 2007 with the information requested above. This information is summarized and reviewed in appropriate sections of this review.

This reviewer initiated a teleconference with the applicant on 05 September 2007 to discuss the draft labeling regarding drug solution preparation as it pertains to the microbiological quality of the constituted drug product. The following applicant representatives were present during this TCON:
This reviewer described his concern regarding the fact that the label describes holding periods (either refrigerated or at room temperature) for product following reconstitution in infusion bags (refer to Section 2.A, package insert of this review). The drug product requires 5 manipulations which penetrate vial and infusion bag container closure systems for preparation of the 250 mg dose. Each of these penetrations poses a risk for contamination of the product with microorganisms. Since the drug product formulation does not include a preservative, there is a possibility of growth of any contaminating microbes in the product during these holding periods prior to its administration. This reviewer requested that the applicant perform some microbial growth studies in the reconstituted product while simulating the storage conditions described in the proposed label. The applicant stated that they would contact colleagues in Japan for the purpose of informing them of this reviewer's concerns, and to discuss carrying out the microbial growth promotion studies.

A second TCON was held on 07 September 2007 between this reviewer and two applicant representatives. The applicant reported that their colleagues in Japan do not wish to do the requested microbial growth study since they do not believe it will generate useful data. Reviewer comments concerning this subject are provided in Section 2.A. of this review.

File Name: N022106R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 22-106 is recommended for approval from the standpoint of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not Applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The manufacturing process is quite complex. The drug substance is manufactured as a powder packaged in bags which are then placed in canisters. . The drug product is then filled into glass vials

B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies identified.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Bryan Riley, Ph.D.

C. CC Block
N/A

30 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

John Metcalfe
9/28/2007 09:17:57 AM
MICROBIOLOGIST

Bryan Riley
9/28/2007 10:02:00 AM
MICROBIOLOGIST