

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-106

MICROBIOLOGY REVIEW(S)

Division of Anti-Infective and Ophthalmology Products

NDA 22-106 SN000
 Doripenem
 Johnson & Johnson

Clinical Microbiology Review #1
 Peter Coderre, PhD
 20 August 2007

APPLICANT:

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SUBMISSION REVIEWED: NDA 22-106 SN000

PROVIDING FOR: The treatment of the following infections caused by susceptible strains of the designated microorganisms:

Complicated intra-abdominal infections caused by *Escherichia coli*

, *Klebsiella pneumoniae*,
Pseudomonas aeruginosa,
Bacteroides fragilis, *Bacteroides*
thetaiotaomicron, *Bacteroides caccae*, *Bacteroides uniformis*, *Bacteroides vulgatus*,
Streptococcus intermedius, *Streptococcus constellatus* and *Peptostreptococcus*
micros.

Complicated urinary tract infections, including pyelonephritis caused by
Escherichia coli, including cases with
 concurrent bacteremia, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus*
mirabilis, *Acinetobacter baumannii*

PRODUCT NAME: Doripenem for Injection

Proprietary: S-4661
 Non-proprietary/USAN: Doripenem
 Compendia: None
 Code name/number: None

CHEMICAL NAME: (+)-(4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-
 [[(3S,5S)-5-(sulfamoylamino)methyl]-3-pyrrolidinyl]thio]-1-azabicyclo[3.2.0]hept-2-
 ene-2-carboxylic acid monohydrate.

STRUCTURAL FORMULA:



MOLECULAR FORMULA: C₁₅H₂₄N₄O₆S₂.H₂O

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DOSAGE AND ROUTE OF ADMINISTRATION:

Infection	Dosage	Frequency	Infusion Time (hours)	Duration
Complicated intra-abdominal infection	500 mg	q8h	1	5-14 days*
Complicated UTI, including pyelonephritis	500 mg	q8h	1	10 days*§

* Duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.

§ Duration can be extended up to 14 days for patients with concurrent bacteremia.

PHARMACOLOGICAL CATEGORY: Antibacterial

DISPENSED: Rx

SUBMISSION DATES:

Received by CDER: 12 December 2006
 Received by Reviewer: 12 December 2006
 Completed by Reviewer: 20 August 2007

RELATED DOCUMENTS: IND 66,416, _____

REMARKS:

Pursuant to the provisions of Section 505(b) of the Federal Food, Drug and Cosmetic Act and Title 21 of the Code of Federal Regulations, 21 CFR §314.50, the Applicant submits an original New Drug Application (NDA) for TRADENAME (Doripenem for Injection) for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections, including _____ pyelonephritis (cUTI).

At the 13 November 2006 teleconference between the Division and the Applicant, agreement was reached that the Microbiology Summary submitted in the original NDA could be replaced to add QC disk data and the corresponding interpretive criteria, and filed as an amendment to the cIAI/cUTI NDA.

The Applicant submitted an amendment to NDA 22-106 (SN001) that contains an updated Microbiology Summary and accompanying datasets in Module 2 and Module 5 respectively, and revised draft labeling in Module 1 that incorporates the new disk data. Reference is made to the 24 April 2007 electronic mail correspondence from the Project Manager requesting the Applicant provide additional microbiology data in support of their pending NDA 22-106. An Amendment to NDA 22-106 that contains the requested microbiology information was submitted and reviewed by this Reviewer.

On 04 June 2007, the Applicant submitted a new amendment to the NDA. Reference was made to the 27 July 2006 pre-NDA meeting between the Applicant and the Division where the Agency agreed to accept an amendment to the cIAI/cUTI NDA in June 2007 that contained pooled breakpoint data from the cIAI, cUTI and nosocomial pneumonia (NP) trials. As such, at this time, the Applicant submitted an updated Microbiology Summary that incorporates new clinical microbiology data from the NP trials, additional data from new animal model studies, updates to the antimicrobial

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spectrum of activity section based on new surveillance data, updates to the Correlation of Provisional Criteria with Clinical Outcome section based on integrated information from the cIAI, cUTI, and NP Phase 3 trials and, new information on the mechanisms of resistance section based on isolates from the NP trials.

RECOMMENDATIONS/CONCLUSIONS

This Reviewer recommends that claims be granted for the following organisms for the following indications:

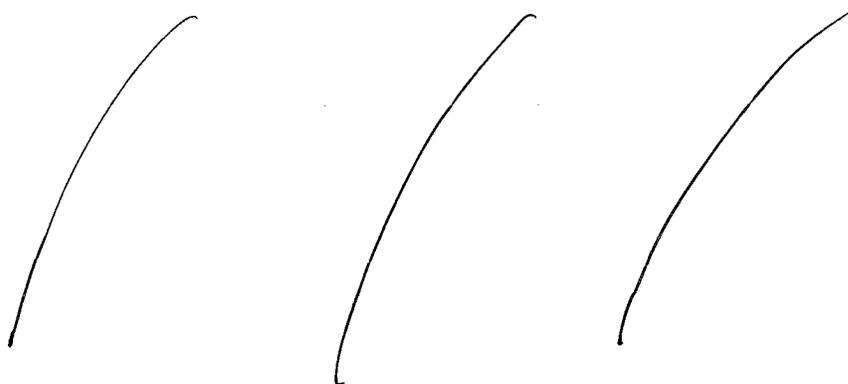
Complicated Urinary Tract Infections (cUTI):

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*
- *Acinetobacter baumannii*

Complicated Intra-abdominal Infections (cIAI):

- *Bacteroides caccae*
- *Bacteroides fragilis*
- *Bacteroides thetaiotaomicron*
- *Bacteroides uniformis*
- *Bacteroides vulgatus*
- *Peptostreptococcus micron*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Streptococcus constellatus*
- *Streptococcus intermedius*

The Applicant proposed the following interpretive criteria:

Applicant's Proposed MIC and Disk Diffusion Interpretive Criteria for Doripenem

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However, this Reviewer recommends the following MIC and disk diffusion interpretive criteria:

Reviewer Recommended Interpretive Criteria

	MIC ($\mu\text{g/ml}$)			Zone Diameter (mm)		
	S ^a	I	R	S	I	R
<i>Enterobacteriaceae</i>	≤ 0.5	--	--	≥ 23	--	--
<i>Pseudomonas aeruginosa</i>	—	--	--	≥ 24	--	--
<i>Acinetobacter baumannii</i>	≤ 1	--	--	≥ 17	--	--
<i>Streptococcus anginosus</i> group (<i>S. constellatus</i> and <i>S. intermedius</i>)	$\leq 0.$	—	--	TBD ^b	--	--
Anaerobes	\leq	—	--	--	--	--

- a. 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.
- b. To Be Determined.

IN SUMMARY, THIS REVIEWER RECOMMENDS **NDA 22-106 IS APPROVABLE** CONTINGENT UPON ACCEPTANCE BY THE APPLICANT OF THE CHANGES MADE TO THE MICROBIOLOGY SECTION OF THE PACKAGE INSERT BY THIS REVIEWER.

The data suggest that the potential for the development of doripenem resistance in *Pseudomonas aeruginosa* may be a safety concern. **Consequently, this Reviewer recommends the Applicant conduct a Phase IV study to examine the occurrence of doripenem resistance in *Pseudomonas aeruginosa*.** This study should consist of two parts.

1. The Applicant should conduct US surveillance studies on *Pseudomonas aeruginosa* isolates over a two year period.
2. The Applicant should conduct additional studies to define these mechanisms more precisely.

In addition, the data suggest that the potential for the development of doripenem resistance in *Klebsiella pneumoniae*, due to the KPC carbapenemase, may be a safety concern. **Consequently, this Reviewer recommends the Applicant conduct a Phase IV study to examine the occurrence of doripenem resistance in *Klebsiella pneumoniae*. Thus, this recommends:**

The Applicant conduct US surveillance studies on *Klebsiella pneumoniae* isolates over a two year period. This should include the monitoring of these isolates for the KPC carbapenemase.

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EXECUTIVE SUMMARY

Doripenem is an injectable, sterile, synthetic, broad-spectrum carbapenem (beta-lactam) antibacterial. The bactericidal mode of action of doripenem and other beta-lactams involves binding to penicillin-binding proteins (PBPs) and inhibiting the biosynthesis of the bacterial cell wall in both Gram-positive and Gram-negative bacteria.

In this new drug application, the Applicant presents data to support the use of Doripenem for Injection in the treatment of subjects 18 years of age or older with:

- **Complicated intra-abdominal infections (cIAI)** caused by *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides caccae*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Streptococcus intermedius*, *Streptococcus constellatus*, and *Peptostreptococcus micros*.
- **Complicated urinary tract infections (cUTI) including pyelonephritis**, caused by *Escherichia coli* (levofloxacin-resistant strains) including cases with concurrent bacteremia, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Enterobacter cloacae*, *Acinetobacter baumannii*, and *Enterococcus faecalis*.

The primary **mechanism of action** of doripenem is the inactivation of penicillin binding proteins (PBPs). While the inactivation of some PBPs (1a, 1b, 2 and 3) contributes to bacterial death, other PBPs (4, 5 and 6) are not essential for bacterial viability and their inactivation by β -lactam antibiotics is not lethal (5). The primary target for doripenem in Gram-negative bacteria is PBP 2.

The Applicant presents data on the binding affinities of various Gram-positive and Gram-negative species to different penicillin binding proteins (PBPs). The data presented show that doripenem had high affinity for PBP 2 (IC₅₀s <0.02 μ g/ml) in two different isolates of *E. coli* and three different isolates of *Pseudomonas aeruginosa*. Thus, these data suggest doripenem should have bactericidal activity against both *Escherichia coli* and *Pseudomonas aeruginosa*. Doripenem had strong affinity for PBP 1 in *S. aureus* Smith and two isolates of *S. pneumoniae*. Again, these data suggest doripenem should have bactericidal activity against both *S. aureus* and *S. pneumoniae*.

The **spectrum of activity** of doripenem covers a variety of aerobic and anaerobic Gram-positive and Gram-negative bacteria. The spectrum of activity includes staphylococci, streptococci, *Enterobacteriaceae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, *Acinetobacter* spp., *Bordetella* spp., *Bacteroides* spp., *Prevotella* spp, *Clostridium* spp., and other Gram-positive anaerobes. MIC₉₀s for these species were usually < 1 μ g/ml. Doripenem was less active against methicillin-resistant *S. aureus* (MRSA), *Enterococcus faecalis*, and was inactive against most isolates of *Enterococcus faecium*, *Corynebacterium* spp. and *Stenotrophomonas maltophilia*.

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Surveillance studies of doripenem susceptibility among clinical isolates were conducted during 2003—2005 in three different geographical regions: North America, Europe and Latin America. In general, MIC90s remained constant or increased by one dilution step over the three years of the surveillance studies for all the organisms surveyed.

However, while MIC90s remained unchanged, there was more variability in MICs from year to year due to increases in the upper end of the MIC ranges for each organism. Oxacillin-susceptible staphylococci and *H. influenzae* demonstrated MIC decreases in the upper end of the MIC ranges over the three year study for all three regions. The increases in the upper end of the MIC ranges tended to occur among the *Enterobacteriaceae*. This was most apparent in isolates from Latin America where increases occurred with isolates of *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *E. cloacae* and *Citrobacter* spp. Increases in MICs were seen among *Enterobacter* spp., *E. cloacae* and *Serratia* spp. isolates from North America. Increases in MICs were seen among *Citrobacter* spp. and *P. mirabilis* isolates from Europe. While these increases in the upper end of the MIC ranges were not MIC90s, these increases may signal potential increases in MIC90s and may warrant monitoring over time.

Doripenem was found to have **synergistic interactions** with several antibiotics. Two studies demonstrated that doripenem could be combined with a range of antimicrobials without risk of antagonism, suggesting that coadministration with other agents would not lead to loss of activity. Doripenem was synergistic when combined with vancomycin or teicoplanin against MRSA. In another study, doripenem was synergistic when combined with amikacin, levofloxacin or cotrimoxazole against *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii*. In the same study, doripenem was also synergistic when combined with daptomycin, levofloxacin, linezolid or vancomycin against MSSA, MRSA, *Enterococcus faecalis* and *S. pneumoniae*.

Carbapenem antibiotics, like other β -lactams, exhibit time-dependent **bactericidal activity**. Bactericidal activity is considered an important attribute in treating acute life-threatening infections. The Applicant presents both MBC and time-kill studies to assess the bactericidal activity of doripenem. In several studies described here, conflicting data are presented regarding bactericidal activity of doripenem.

The Applicant presents data from three time-kill studies for 18 bacterial isolates (8 different species). The greatest bactericidal activity was seen against the Gram-positive isolates, *S. aureus* and *S. pneumoniae* with the exception of *E. faecalis* to which doripenem was bactericidal over long (24 hours) but not short periods of time (8 hours).

Doripenem demonstrated the least amount of bactericidal activity against the Gram-negatives e.g. *Enterobacteriaceae* (*E. coli*, *K. pneumoniae* and *E. cloacae*) particularly the non-fermenters (*P. aeruginosa* and *A. baumannii*). **The reduced bactericidal activity against the Enterobacteriaceae and non-fermentative Gram-negatives e.g. P. aeruginosa, are of concern as these are key pathogens in the indications sought i.e. cUTI and cIAI.**

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Doripenem exhibits a species-dependent **postantibiotic effect (PAE)** both *in vitro* and *in vivo*. *In vitro*, a moderate PAE (1.9 to 2 h) was observed against *S. aureus* and *P. aeruginosa*. As with other carbapenems, the PAE was typically short against species such as *E. coli* and *K. pneumoniae* (less than 1 h). In an additional study, the *in vitro* PAE versus *P. aeruginosa* was relatively short (0.8 h) but was roughly comparable to meropenem (1.1 h).

In contrast, a prolonged PAE was shown *in vivo* in two animal models. In a neutropenic mouse thigh model, doripenem exhibited a PAE that ranged from 7.8 to 8.0 h for *S. aureus* and *P. aeruginosa* to 5 h for *K. pneumoniae*. In a neutropenic mouse respiratory infection model, the PAE of doripenem against a ceftazidime-resistant *P. aeruginosa* was greater than 6 h.

The antimicrobial efficacy and **lipopolysaccharide (LPS) release** following treatment with doripenem, meropenem-cilastatin, imipenem-cilastatin, and ceftazidime was evaluated in a neutropenic rat model of bloodstream infection. Doripenem produced the lowest serum LPS concentration of any of the carbapenems tested at 1 and 3 h.

The predominant **mechanism of resistance** to carbapenems in Gram-positive bacteria is reduced affinity for altered penicillin binding proteins (PBPs). The presence of carbapenemases, AmpC cephalosporinase overexpression, and altered permeability and efflux are the predominant mechanisms of carbapenem resistance in Gram-negative bacteria.

The most common mechanism described for carbapenem resistance in *P. aeruginosa* is the loss or reduced expression of the outer membrane protein OprD55, frequently coupled with the β -lactamase-mediated resistance related to the upregulation of the chromosomal AmpC, found in as many as 72% of imipenem-resistant *P. aeruginosa* isolates.

Reduced susceptibility associated with elevated levels of AmpC, in combination with porin loss, has also been described in *K. pneumoniae*, *E. cloacae* and *Proteus rettgeri*. In *K. pneumoniae*, an increase in the Class A carbapenemases of the KPC family has also occurred in the past few years, initially in the New York City area, but spreading to other regions in the US and other countries. Doripenem MICs for these isolates ranged from 2 $\mu\text{g/ml}$ to > 128 $\mu\text{g/ml}$. This MIC range should be of concern and is much higher than the MIC₉₀ = 0.06 $\mu\text{g/ml}$ seen in surveillance studies. **This Reviewer recommends that all future *K. pneumoniae* isolates be screened for the presence of the KPC carbapenemase.**

In the US, isolates expressing metallo- β -lactamases are extremely rare at this time, but production of these enzymes varies considerably worldwide.

The Applicant presents the results of multiple passage studies on one isolate each of *S. aureus*, *E. coli* and *P. aeruginosa*. The results indicate doripenem MICs increased by 6, 3 and 6 dilution steps when passaged in *S. aureus*, *E. coli* and *P. aeruginosa*, respectively.

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The results of the serial passage study and the multiple passage studies with *P. aeruginosa* are a cause for concern that resistance may develop in future clinical isolates.

To test the *in vivo* efficacy of doripenem, the Applicant explored several **animal models of efficacy**. In a standard mouse protection peritonitis model, doripenem demonstrated therapeutic effectiveness against both Gram-positive and Gram-negative bacterial infections. For a majority of the isolates tested, the dose demonstrating efficacy in 50% of animals (ED50) of doripenem was low, regardless of whether it was administered as a single dose, or two to three sequential doses; however more drug was usually required for a single dose to achieve efficacy.

In addition, the Applicant explored the efficacy of doripenem in a murine neutropenic thigh infection model. Doripenem displayed dose-related effectiveness with respect to reduction of bacterial burden and increase in survival rate. In a urinary tract model, doripenem was efficacious against pathogens such as CAZ-resistant *P. aeruginosa*. In all animal models evaluated, the efficacy of doripenem was generally equal to or better than those of the control agents such as imipenem, meropenem, and ceftazidime.

The Applicant has determined **pharmacokinetics in a variety of animals** including mice, rats, rabbits, dogs, monkeys and humans. When dosed at 20 mg/kg, the AUC ranged from 9.3 mg·hr/ml in rats to 79.5 mg·hr/ml in humans while the t_{1/2} ranged from 0.1 hr in rats to 1.0 hr in humans. In mice, the highest concentrations of drug were in plasma. Plasma protein binding in all species ranged from 6.1 to 35.2% with a binding of 8.1% in humans. Doripenem was metabolized to a microbially inactive metabolite, M-1. The predominant excretion pathway was by the urinary tract.

The *in vitro* activity of doripenem versus meropenem against clinical isolates of *E. coli*, *S. aureus* and *P. aeruginosa* was assessed in an ***in vitro* pharmacodynamic model** that simulated human pharmacokinetics following intravenous dosing. All dosing simulations with doripenem and meropenem resulted in the elimination of *S. aureus* SR20406 or *E. coli* SR21262 beyond the limit of detection within 8 h, and no re-growth of bacteria was observed. No increased efficacy was noted by increasing the quantity of compound or the dosing frequency. **For *P. aeruginosa* isolates displaying doripenem MICs of 4 µg/ml, an increase in activity was observed by changing the dosing regimen to three times a day from two times a day, thus increasing the T > MIC. In isolates with higher MICs, increasing the amount of compound also improved efficacy.**

The ***in vivo* pharmacodynamic activities** of doripenem were characterized in a mouse neutropenic thigh infection model against several Gram-positive and Gram-negative bacterial pathogens. These PK/PD studies revealed that the time above the MIC (T > MIC) was the pharmacokinetic parameter that clearly correlated with *in vivo* efficacy. The magnitude of the PK/PD parameter required to achieve a static effect was relatively similar for the tested bacterial isolates, which included *S. pneumoniae*, *S. aureus*, *E. coli*, *K. pneumoniae*, *E. cloacae* and *P. aeruginosa*. The time above MIC required to achieve a static effect and a 1 log₁₀ reduction for *P. aeruginosa* was 23% and 28%, respectively.

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The Applicant presents the results of several studies of **human pharmacokinetics and pharmacodynamics**. Doripenem binds to human plasma protein at a low rate of 8.1%. With a large proportion of the drug free in plasma, much of the drug is potentially available for tissue and fluid penetration. The median doripenem steady-state volume of distribution in healthy adults was 16.6 L, approximately the extracellular fluid volume in humans (18.2 L). Doripenem concentrations ranged from 1 to 2 µg/ml in most tissues, thus exceeding the MIC for most susceptible bacteria. The drug is metabolized to produce a microbiologically inactive compound, doripenem M-1. Doripenem is rapidly eliminated with a mean $t_{1/2}$ = 69 min that is independent of the dose or duration of intravenous infusion. The main route of elimination is via the urinary tract.

The $T > MIC$ is the pharmacokinetic/pharmacodynamic parameter for doripenem that best correlates with therapeutic efficacy. The $T > MIC$ values required to achieve a bacteriostatic effect are approximately 30% of the dosing interval.

Monte Carlo simulations were used to determine species specific PK/PD target attainments for pathogens responsible for cUTI or cIAI. These data demonstrate that target attainments of 25-35% for these pathogens e.g., *Enterobacteriaceae*, non-*Enterobacteriaceae*, *Staphylococcus* spp., *S. pneumoniae*, and *Streptococcus* spp. other than *S. pneumoniae*, were in the range considered of relevance for *in vivo* efficacy (generally >80%). However, target attainment for *Enterococcus* spp. was below 80%; a subanalysis for *E. faecalis* indicated a greater target attainment rate, 82.2, 67.5 and 54.5% for $T > MIC$ s of 25, 30 and 35%, respectively, but most $T > MIC$ values were below the relevant rate of 80%.

The Applicant has established both broth dilution and disk diffusion susceptibility testing quality control parameters. These values are presented here:

^a NA = Not applicable

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

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

Organism	Doripenem		Levofloxacin	
	Clinical Cure (%)	Bacterial Eradication (%)	Clinical Cure (%)	Bacterial Eradication (%)
Gram-negative aerobes				
<i>Acinetobacter baumannii</i>	10/10 (100)	8/10 (80)	0/1 (0)	0/1 (0)
<i>Enterobacter cloacae</i>	22/28 (79)	13/23 (54)	3/7 (43)	3/7 (43)
<i>Escherichia coli</i>	31/32 (97)	31/35 (88)	19/20 (94)	18/21 (87)
<i>Klebsiella pneumoniae</i>	29/32 (91)	26/33 (79)	4/7 (57)	5/8 (63)
<i>Proteus mirabilis</i>	29/30 (97)	22/30 (73)	13/15 (87)	13/15 (87)
<i>Pseudomonas aeruginosa</i>	23/24 (96)	17/24 (71)	5/6 (83)	5/7 (71)
Gram-positive aerobes				
<i>Staphylococcus faecalis</i>	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.

The Applicant seeks label claims for the following pathogens: *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 *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, levofloxacin 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*.**

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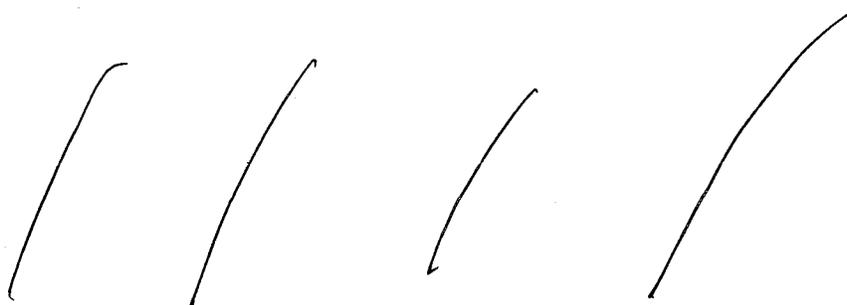
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Patients infected with *P. aeruginosa* and treated with doripenem had clinical cure and bacteriologic eradication rates of 96% and 71%, respectively, while patients treated with levofloxacin had clinical cure and bacteriologic eradication rates of 83% and 71%, respectively; these represent differences of 13% for clinical cure and 0% for bacteriologic eradication rates. Also, Monte Carlo simulation data (see Table 30) indicate that the probability of target attainment is below the range considered relevant to *in vivo* efficacy ($\geq 80\%$) 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 *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. Thus, **this Reviewer recommends that the Applicant be granted claims for *A. baumannii*.**



The Applicant presents data from cUTI studies showing the clinical and microbiologic outcomes at each MIC for Gram-negative aerobic 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 $\mu\text{g/ml}$ which was also the MIC mode. All of these isolates had a MIC value of ≤ 2 $\mu\text{g/ml}$. Among *E. cloacae* isolates, 93% (27/29) had a MIC value of ≤ 0.5 $\mu\text{g/ml}$ which was also the MIC mode. All of these isolates had a MIC value of ≤ 1 $\mu\text{g/ml}$. Among *E. coli* isolates, 90% (301/335) had a MIC value of ≤ 0.03 $\mu\text{g/ml}$ which was also the MIC mode. All of these isolates had a MIC value of ≤ 0.12 $\mu\text{g/ml}$. Eighty-eight percent (23/26) of the *K. pneumoniae* isolates had a MIC of ≤ 0.12 $\mu\text{g/ml}$. The mode MIC was 0.06 $\mu\text{g/ml}$. Among *P. mirabilis* isolates, 90% (27/30) had MIC values of 0.12– 0.5 $\mu\text{g/ml}$. Among *P. aeruginosa* isolates, 92% (22/24) had MICs ≤ 8 $\mu\text{g/ml}$. MIC values were evenly distributed across a range of ≤ 0.03 and 16 $\mu\text{g/ml}$. 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 $\mu\text{g/ml}$, MICs among *P. aeruginosa* isolates were relatively evenly distributed. Thus, there was little correlation of MIC with clinical or bacteriologic outcome.

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The Applicant presents data from cUTI studies showing the clinical and microbiologic outcomes at each MIC for one Gram-positive aerobic organism, *E. faecalis*. About 92% (11/12) of the *E. faecalis* isolates had a MIC of ≤ 4 $\mu\text{g/ml}$. Most isolates had a MIC value of either 2 or 4 $\mu\text{g/ml}$. Again, there was little correlation of MIC with clinical or bacteriologic outcome.

The Applicant presents clinical and bacteriologic outcome data from two trials for a variety of pathogens isolated from patients with **complicated intra-abdominal infections (cIAI)** treated with either doripenem or meropenem. The data is summarized in Table B.

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

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

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. 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. 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%. **Consequently, this Reviewer recommends the Applicant be granted claims for both *B. fragilis* and *B. uniformis*.**

However, patients infected with either *B. caccae*, *B. thetaiotaomicron* or *P. micros* and treated with doripenem had lower clinical cure and bacteriologic eradication rates than patients infected with one of these pathogens and treated with

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meropenem. Patients infected with *B. caccae* and treated with doripenem had clinical cure and bacteriologic eradication rates of 86% and 92%, respectively, while patients treated with meropenem had clinical cure and bacteriologic eradication rates of 95% representing differences of 9% for clinical cure and 3% for bacteriologic eradication. Similarly, patients infected with *B. thetaiotaomicron* and treated with doripenem had clinical cure and bacteriologic eradication rates of 79% and 88%, respectively, while patients treated with meropenem had clinical cure and bacteriologic eradication rates of 86% and 89%, respectively, representing differences of 7% for clinical cure and 1% for bacteriologic eradication. 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. Consequently, since clinical cure rates for patients treated with doripenem infected with any of these three pathogens was at least 7% lower than patients from the meropenem cohort. **This Reviewer recommends that the Applicant be granted claims for *B. caccae*, *B. thetaiotaomicron*, and *P. micros*.**

Patients infected with *B. vulgatus* and treated with doripenem had clinical cure and bacteriologic eradication rates of 100%, while patients treated with meropenem had clinical cure and bacteriologic eradication rates of 75% representing differences of 25% for both clinical cure and bacteriologic eradication rates. Thus, **this Reviewer recommends that the Applicant be granted claims for *B. vulgatus*.**

The Applicant seeks label claims for three Gram-negative facultative 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 *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 both *E. coli* and *P. aeruginosa*.**

However, 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. **This Reviewer recommends that the Applicant be granted a claim for *K. pneumoniae*.**

The Applicant seeks label claims for three Gram-positive aerobic pathogens including *S. constellatus* and *S. intermedius*. Compared to meropenem treated

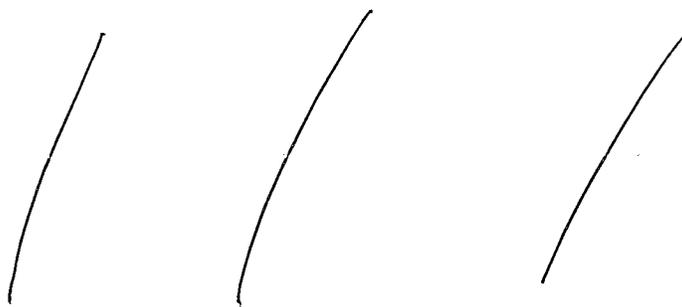
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patients, doripenem treated patients had higher clinical cure and bacteriologic eradication rates for patients infected with either *E. faecalis* or *S. intermedius*. Patients infected with *S. intermedius* and treated with doripenem had clinical cure 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. intermedius*.**

Patients infected with *S. constellatus* and treated with doripenem had lower clinical cure and bacteriologic eradication rates than patients treated with meropenem. Patients infected with *S. constellatus* and treated with doripenem had clinical cure and bacteriologic eradication rates of 90%, while patients treated with meropenem had clinical cure and bacteriologic eradication rates of 71% representing differences of 19% for clinical cure and for bacteriologic eradication. Thus, **this Reviewer recommends that the Applicant be granted claims for *S. constellatus*.**



The Applicant presents the results of clinical cure and bacteriologic eradication rates for patients infected with a wide variety of organisms stratified by different doripenem MICs.

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 $\mu\text{g/ml}$. Among *B. fragilis* isolates, 89% (56/63) had a MIC value of ≤ 0.25 $\mu\text{g/ml}$. Almost 94% of *B. thetaiotaomicron* isolates (30/32) had MICs ≤ 0.5 $\mu\text{g/ml}$. Among *B. vulgatus* isolates, 95% (20/21) had MICs ≤ 0.5 $\mu\text{g/ml}$. Finally, all *P. micros* isolates had MICs of ≤ 0.25 $\mu\text{g/ml}$. 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 $\mu\text{g/ml}$. 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 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 $\mu\text{g/ml}$. All of these isolates had a MIC value of ≤ 0.12 $\mu\text{g/ml}$ and the MIC mode was ≤ 0.03 $\mu\text{g/ml}$. Among *K. pneumoniae* isolates, 97% (29/30) had a

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MIC value of ≤ 0.06 $\mu\text{g/ml}$ which was also the MIC mode. All of these isolates had a MIC value of ≤ 0.12 $\mu\text{g/ml}$. Among *P. aeruginosa* isolates, 95% (36/38) had MICs ≤ 1 $\mu\text{g/ml}$. Only 34% (13/38) of isolates has a MIC of ≤ 0.12 $\mu\text{g/ml}$. 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 $\mu\text{g/ml}$, MICs among *P. aeruginosa* isolates were relatively evenly distributed. Overall, there was little correlation of MIC with clinical or bacteriologic outcome.

The Applicant presents 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 $\mu\text{g/ml}$. Most isolates had a MIC value of either 2 or 4 $\mu\text{g/ml}$ there was no MIC mode. Among *S. constellatus* isolates, 90% (9/10) had a MIC value of ≤ 0.06 $\mu\text{g/ml}$ while the MIC mode was ≤ 0.03 $\mu\text{g/ml}$. All of these isolates had a MIC value of ≤ 0.12 $\mu\text{g/ml}$. Among *S. intermedius* isolates, 94% (34/36) had MICs ≤ 0.03 $\mu\text{g/ml}$. 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 $\mu\text{g/ml}$ and evenly distributed, the MIC mode for *S. intermedius* isolates was much lower (≤ 0.03 $\mu\text{g/ml}$). Again, there was little correlation of MIC with clinical or bacteriologic outcome.

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 β -lactamases, and higher β -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 β -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 doripenem resistance occurrence on 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.

Consequently, this Reviewer recommends that claims be granted for the following organisms for the following indications:

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Complicated Urinary Tract Infections (cUTI):

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*
- *Acinetobacter baumannii*

Complicated Intra-abdominal Infections (cIAI):

- *Bacteroides caccae*
- *Bacteroides fragilis*
- *Bacteroides thetaiotaomicron*
- *Bacteroides uniformis*
- *Bacteroides vulgatus*
- *Peptostreptococcus micron*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Streptococcus constellatus*
- *Streptococcus intermedius*

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 [6].

The Applicant supplied correlation of MIC and disk diffusion data in the form of scattergrams for *E. coli* and *P. aeruginosa*. 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 this organism.

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

	S ^a	MIC (µg/ml)			Zone Diameter (mm)		
		I	R	S	I	R	
<i>Enterobacteriaceae</i>	≤ 0.5	--	--	≥ 23	--	--	
<i>Pseudomonas aeruginosa</i>	≤ 1	--	--	≥ 24	--	--	
<i>Acinetobacter baumannii</i>	≤ 1	--	--	≥ 17	--	--	
<i>Streptococcus angiosus</i> group (<i>S. constellatus</i> and <i>S. intermedius</i>)	≤ 0	--	--	TBD ^b	--	--	
Anaerobes	—	--	--	--	--	--	

- a. 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.
- b. To be determined.

IN SUMMARY, THIS REVIEWER RECOMMENDS NDA 22-106 IS APPROVABLE CONTINGENT UPON ACCEPTANCE BY THE APPLICANT OF THE CHANGES MADE TO THE MICROBIOLOGY SECTION OF THE PACKAGE INSERT BY THIS REVIEWER.

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IN ADDITION, THE APPLICANT SHOULD AGREE TO A PHASE 4 COMMITMENT INVOLVING MONITORING OF DORIPENEM RESISTANCE IN *PSEUDOMONAS AERUGINOSA* BASED UPON THE FOLLOWING DATA:

- *In vitro* susceptibility data demonstrate that multidrug-resistant cystic fibrosis isolates displayed elevated MIC₉₀ values of 32 µg/ml and 64 µg/ml for mucoid and non-mucoid isolates, respectively. *P. aeruginosa* isolates with metallo-β-lactamases demonstrated MIC₉₀ values of > 64 µg/ml.
- Doripenem had the least amount of bactericidal activity against non-fermentative Gram-negative bacteria, particularly *P. aeruginosa* and *A. baumannii*.
- The results of a serial passage study showed that selection with doripenem led to MIC increases that were >8-fold in three isolates, 2-fold in one isolate and were unchanged in two isolates. Selection with doripenem and gentamicin resulted in one isolate with a 4-fold doripenem MIC increase, two isolates with a 2-fold increase and three isolates with unchanged MIC values. The results of multiple passage studies on one isolate each of *P. aeruginosa* as indicated indicate doripenem MICs increased by 6 dilution steps when passaged in *P. aeruginosa*.
- *In vitro* pharmacodynamic modeling demonstrated that for isolates with doripenem MICs of 4 µg/ml, an increase in activity was observed by changing the dosing regimen from two to three times a day, thus increasing the T>MIC. In isolates with higher MICs, increasing the amount of compound also improved efficacy.
- Monte Carlo simulation data 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.
- In the cUTI clinical trials, 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%; the difference between clinical cure and bacteriologic eradication rates was 13%.
- A study to elucidate the mechanisms of resistance among pairs of clinical isolates that demonstrate at least a two step increase in doripenem MICs between baseline and on therapy treatment showed that two pairs of *P. aeruginosa* isolates exhibited changes in efflux and porin genes, in addition to changes in β-lactamase activity.

AS THESE INCREASES IN DORIPENEM SUSCEPTIBILITY ON THERAPY ARE A SAFETY CONCERN, THIS PHASE 4 STUDY SHOULD CONSIST OF TWO PARTS.

1. The Applicant should conduct US surveillance studies on *Pseudomonas aeruginosa* isolates over a two year period.
2. The Applicant should conduct additional studies to define these mechanisms more precisely.

In addition, the data suggest that the potential for the development of doripenem resistance in *Klebsiella pneumoniae*, due to the KPC carbapenemase, may be a safety concern. **Consequently, this Reviewer recommends the Applicant conduct a Phase IV study to examine the occurrence of doripenem resistance in *Klebsiella pneumoniae*. Thus, this Reviewer recommends:**

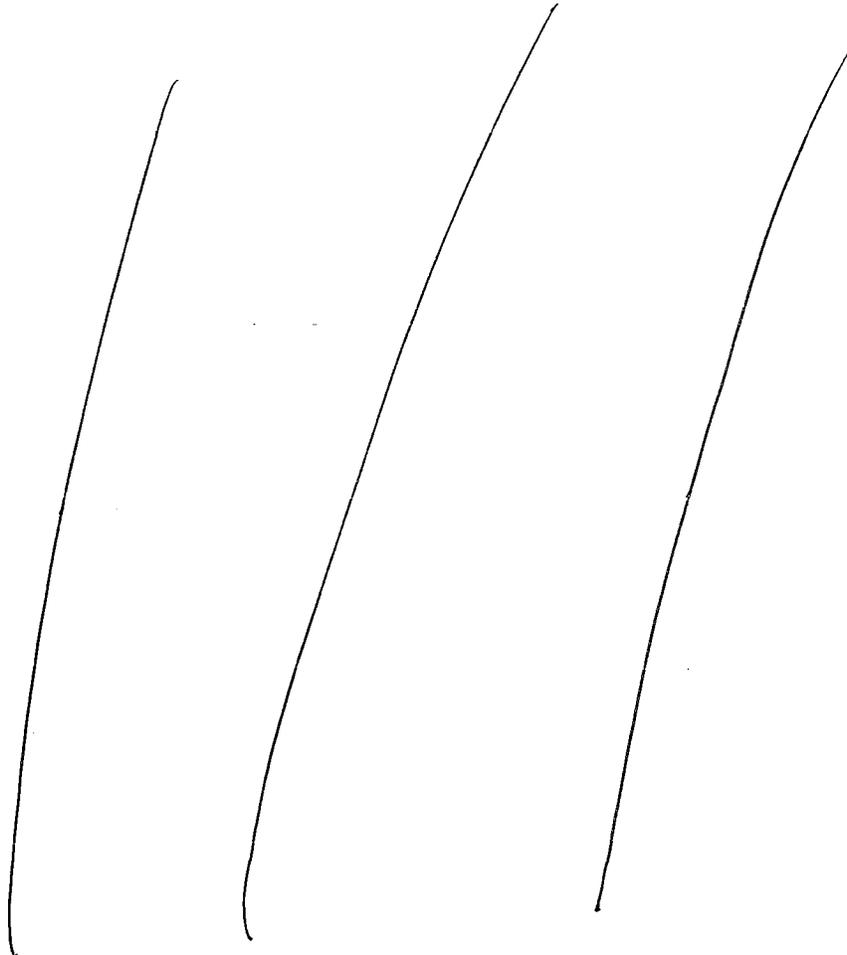
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The Applicant should conduct US surveillance studies on *Klebsiella pneumoniae* isolates over a two year period. This should include the monitoring of these isolates for the KPC carbapenemase.

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INTRODUCTION

Doripenem is an injectable, sterile, synthetic, broad-spectrum carbapenem (beta-lactam) antibacterial. The bactericidal mode of action of doripenem and other beta-lactams involves binding to penicillin-binding proteins (PBPs) and inhibiting the biosynthesis of the bacterial cell wall in both Gram-positive and Gram-negative bacteria.

In this new drug application, Johnson & Johnson Pharmaceutical Research & Development, L.L.C (J&JPRD; the Applicant) presents data to support the use of Doripenem for Injection in the treatment of subjects 18 years of age or older with:

- **Complicated intra-abdominal infections (cIAI) caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides caccae*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Streptococcus intermedius*, *Streptococcus constellatus*, and *Peptostreptococcus micros*.**
- **Complicated urinary tract infections (cUTI) including pyelonephritis, caused by *Escherichia coli* including cases with concurrent bacteremia, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Acinetobacter baumannii*, and**

Complicated intra-abdominal infections are commonly encountered in general surgery, and require both operative drainage and empiric, broad-spectrum antibacterial therapy. Since antibacterial therapy must be initiated before culture results are available, the antibacterial agent chosen must cover Gram-positive aerobic, Gram-negative aerobic and anaerobic bacteria that comprise the usual gastrointestinal (GI) flora. The pathogens most frequently encountered in cIAI include *E. coli*, *K. pneumoniae*, *S. pneumoniae*, other streptococcal species [1]. Only 6% of peritonitis patients had disease caused by anaerobes including *B. fragilis*, other *Bacterioids* spp. and *Peptostreptococcus* spp. Because the mortality rate and other complications from cIAI can be high, effective management of these infections requires early diagnosis, appropriate surgical intervention and treatment with an optimal antibacterial agent with a spectrum of activity to cover these pathogens.

A recent report of *in vitro* susceptibilities of aerobic and facultative Gram-negative bacilli isolated from subjects with IAI worldwide identified 5,658 aerobic and facultative Gram-negative bacteria [2]. *Enterobacteriaceae* composed 84% of the total isolates. Among the antibacterial agents tested, the carbapenems were the most consistently active against *Enterobacteriaceae*. The most common IAI isolate was *E. coli* (46%), and the susceptibility rate to the quinolones (70% to 90% susceptible), extended spectrum cephalosporins (80% to 97% susceptible), aminoglycosides (77% to 100% susceptible), and carbapenems (99% to 100% susceptible) tested varied among geographic regions,

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with isolates from the Asia/Pacific region generally being the most resistant [2]. Due to the broad spectrum of antibacterial activity against aerobic and anaerobic pathogens that cause cIAI, the Applicant expects that doripenem would be effective in the treatment of these cIAIs, including those caused by pathogens resistant to other antibacterial agents.

Urinary tract infections (UTIs) are associated with a high risk of morbidity, especially in the elderly population, and are the leading cause of Gram-negative bacteremia in subjects of all ages. Complicated lower UTIs (cLUTIs) occur in subjects with a functionally, metabolically, or anatomically abnormal urinary tract and range from cystitis to life-threatening urosepsis. The predisposing conditions that constitute functional or anatomical abnormalities of the urinary tract include the presence of an indwelling catheter, increased residual urine after voiding or neurogenic bladder, obstructive uropathies such as nephrolithiasis or fibrosis, and urinary retention in men, often due to benign prostatic hypertrophy.

Pyelonephritis, which is often accompanied by bacteremia, is characterized by the presence of systemic and local signs and symptoms of an ongoing infection, (e.g., malaise, chills, fever, back pain, and flank pain). Pyelonephritis can be either complicated (i.e., associated with predisposing anatomical or functional abnormality of the urinary tract) or uncomplicated. Although complicated pyelonephritis has not been commonly emphasized in previous publications or regulatory submissions, the distinction between complicated and uncomplicated pyelonephritis has the same significance as for lower UTIs.

The type and duration of antibacterial therapy for both pyelonephritis and cLUTI are the same and, therefore, these diseases were studied together under the complicated UTI (cUTI) indication. Complicated UTIs are caused by a broad range of bacteria, many of which are becoming increasingly resistant to multiple antibacterial agents. For this reason, the carbapenems may serve as an alternative for the treatment of subjects with cUTI requiring parenteral antibacterial therapy. Empiric treatment of cUTI with a broad spectrum antibacterial agent, before urine culture results are available, can help avoid the unnecessary costs of treatment failures, disease progression, subject re-evaluations, return visits, subject dissatisfaction, and the costs associated with initiating a second course of antibacterial therapy.

E. coli is responsible for 95% of all cUTIs [3]. In recurrent UTIs, particularly in the presence of structural abnormalities of the urinary tract, the relative frequency of infection increases greatly and is caused by *Proteus*, *Pseudomonas*, *Klebsiella*, *Enterobacter* spp., staphylococci and enterococci.

A recent study from the North American UTI Collaborative Alliance on antibiotic resistance in *E. coli* outpatient urinary isolates reported results in the United States (US) and Canada from April 2003 to June 2004 [4]. Of the 1,142 *E. coli* isolates collected, 862 (76%) and 280 (25%) were collected from the US and Canada, respectively. Overall,

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resistance to ampicillin was 37.7%, followed by trimethoprim/sulfamethoxazole (21.3%), ciprofloxacin (5.5%), levofloxacin (5.1%), and nitrofurantoin (1.1%). Furthermore, *E. coli* resistance rates for all antibacterial agents tested were higher in US medical centers compared with Canadian medical centers. Resistance rates were highest in subjects aged \geq 65 years [4].

Quinolones are the most commonly prescribed antibacterial agents used to treat cUTI and the increasing numbers of quinolone-resistant pathogens creates a need for newer, broad-spectrum antibacterial agents for use in this indication. In addition, subjects with cUTI often have other infections and confounding disease, requiring treatment with potent broad-spectrum antibacterial agents. Due to the high urinary concentrations of doripenem and its bactericidal activity against key bacterial pathogens of cUTI, including *E. coli*, *Klebsiella* spp., other *Enterobacteriaceae*, and *P. aeruginosa*, the Applicant expects that doripenem would successfully treat cUTI, including those infections caused by pathogens resistant to other therapies.

For the treatment of both cIAI and cUTI, the carbapenems may become an alternative for first-line antibacterial therapy, because they can be used as monotherapy due to their broad spectrum of activity against the most common causative pathogens.

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PRECLINICAL EFFICACY—*IN VITRO***MECHANISM OF ACTION**

The targets of β -lactam antibiotics, including carbapenems such as doripenem, are penicillin-binding proteins (PBPs), membrane-associated bacterial enzymes involved in the last steps of peptidoglycan (cell wall) biosynthesis. β -lactams exert their antibacterial effect by covalently binding to the active-site serine residues of the penicilloyl serine transferase (transpeptidase). The resulting covalently modified acyl enzyme is inactive for the time required for cell division, thereby inhibiting peptidoglycan cross-linking and causing cell death.

Doripenem exerts its antibacterial activity by binding to essential PBPs in both Gram-positive and Gram-negative bacteria. In Gram-negative bacteria, doripenem behaves like other carbapenems with high affinity for PBP 2 in both *E. coli* and *P. aeruginosa*. In the latter organism there is comparable binding to PBP 3 also, although the morphological change associated with doripenem exposure was the formation of spherical cells, compatible with PBP 2 binding.

In *S. aureus* doripenem binds with highest affinity to PBPs 1 and 4 with IC₅₀ values < 0.1 μ g/ml. Doripenem binds very tightly to all PBPs in a penicillin-susceptible *S. pneumoniae* with IC₅₀ values <0.02 μ g/ml, but has IC₅₀ values at least an order of magnitude higher in a penicillin-resistant isolate.

PBPs from Gram-Negative Bacteria

Carbapenems in general have high affinity for multiple PBPs in Gram-negative bacteria. The PBPs of primary importance are the high-molecular weight class A PBP 1a and PBP 1b, PBPs whose function is related to lytic activity, and the high-molecular weight class B PBP 2 and PBP 3, whose functions are associated with cell shape.

Carbapenems show the greatest affinity for PBP 2. Variations in PBP affinities exist depending on the particular carbapenem. For example, in *Escherichia coli*, imipenem and meropenem both have highest affinity for PBP 2 and PBP 4. Meropenem also has moderate affinity for PBP 3, while imipenem has lower affinity for PBP 3 than for the other high molecular weight PBPs. Both carbapenems bind to PBP 1a, PBP 1b or both with slightly lower affinity than for PBP 2, such that the first morphological change of the cells is to become spherical, followed by cell lysis when higher drug levels are achieved.

Data from two studies showed that doripenem, like imipenem and meropenem, had high affinity for PBP 2 (IC₅₀s <0.02 μ g/ml) in two different isolates of *E. coli* (Table 1). Affinities for PBP 1b and PBP 3 were similar for doripenem (ranging from 1.2 to 2 μ g/ml).

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Table 1. Binding of Doripenem, Imipenem and Meropenem to PBPs from Gram-Negative Bacteria

Organism	Isolate	IC50 (µg/ml)			for PBP:			
		1a	1b	2	3	4	5	6
<i>E. coli</i>	NIHJ JC-2	> 4	1.2	< 0.02	1.8	1.6	> 4	> 4
<i>E. coli</i>	MC4100	2	2	0.008	2	0.02	4	1
<i>P. aeruginosa</i>	ATCC 25619	0.4	0.67	0.13	0.088	< 0.02	> 4	> 4
<i>P. aeruginosa</i>	ATCC 27853	0.5	0.3	0.06	0.06	< 0.008	> 4	> 4
<i>P. aeruginosa</i>	PAO-1	0.5	0.5	0.06	0.1	0.008	8	8

*Concentration of carbapenem that inhibited the binding of Bicillin FL by 50%.

Source: Table 11, this submission.

Data from two studies showed that doripenem had good affinity for both PBP 2 and PBP 3 (IC50s = 0.13 µg/ml) in three different isolates of *Pseudomonas aeruginosa* (Table 1). Doripenem affinity for PBP 1a and PBP 1b was 3 to 10-fold less than for PBP 2 and PBP 3 (Table 1). In both *E. coli* and *P. aeruginosa* doripenem had high affinity (IC50s = 0.02 µg/ml) for the low-molecular weight nonessential PBP4 in four out of the five isolates tested, but not for PBP 5 and PBP 6 (Table 1).

In Gram-negative bacteria, the inhibition of PBP 2 causes changes in cell morphology leading to the formation of spherical cells, whereas inhibition of PBP 3, leads to filamentation. Incubation of *P. aeruginosa* isolate PAO-1 for 2 h in the presence of 1X MIC of doripenem led to the formation of spherical cells [7]. This result, along with the IC50 data, indicates that PBP 2 is the primary target in Gram-negative bacteria.

PBPs from Gram-Positive Bacteria

Staphylococcus aureus generally produces four PBPs, three high molecular weight (PBP 1, PBP 2, PBP 3) and one low molecular weight (PBP 4). Cephalosporins preferentially bind to PBP 2 or PBP 3 depending on the particular drug while carbapenems have the highest affinity for PBP1. Doripenem has been shown to have high affinity for PBP 1 (IC50 = 0.078 µg/ml) in methicillin-susceptible *S. aureus* Smith (Table 2). Doripenem also had good affinity for PBP 4 (IC50 = 0.11 µg/ml) (Table 2). Doripenem had poor affinity for PBP 3.

Streptococcus pneumoniae has six PBPs, five high molecular weight (three class A PBP 1a, PBP 1b, and PBP 2a; and two class B PBP 2x and PBP 2b) and one low molecular weight (PBP 3). PBP 2x is the primary target for cephalosporins and PBP 2b is the primary target for penicillins. PBP 1a also is an important target for both types of β-lactams. Doripenem had low IC50s (= 0.02 µg/ml) for all PBPs in a penicillin-susceptible isolate of *S. pneumoniae* (Table 2). The doripenem IC50 increased for all PBPs except PBP 3 in a penicillin-resistant isolate, with the largest increases (>100-fold) occurring for PBP 2b and PBP 2x.

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Table 2. Binding of Doripenem, Imipenem and Meropenem to PBPs from Gram-Positive Bacteria

Organism	Isolate	IC50			PBP:		
		1	2	(µg/ml) 3	for 4	5	6
<i>S. aureus</i> methicillin-susceptible	Smith	0.078	1.5	> 4	0.11		
		1a	1b	2x	2a	2b	3
<i>S. pneumoniae</i> penicillin-susceptible	8865	0.007	0.005	0.02	0.02	0.01	0.01
<i>S. pneumoniae</i> penicillin-resistant	8819	0.2	0.1	3.7	0.2	2	< 0.02

*Concentration of carbapenem that inhibited the binding of Bicillin FL by 50%.

Source: Table 12, this submission.

Reviewer's comments: While the inactivation of some PBPs (1a, 1b, 2 and 3) contributes to bacterial death, other PBPs (4, 5 and 6) are not essential for bacterial viability and their inactivation by β -lactam antibiotics is not lethal (1). The primary target for doripenem in Gram-negative bacteria is PBP 2.

The Applicant presents data on the binding affinities of various Gram-positive and Gram-negative species to different penicillin binding proteins (PBPs). The data presented show that doripenem had high affinity for PBP 2 (IC50s <0.02 µg/ml) in two different isolates of *E. coli* and three different isolates of *Pseudomonas aeruginosa*. Thus, these data suggest doripenem should have bactericidal activity against both *E. coli* and *Pseudomonas aeruginosa*. Doripenem had strong affinity for PBP 1 in *S. aureus* Smith and two isolates of *S. pneumoniae*. Again, these data suggest doripenem should have bactericidal activity against both *S. aureus* and *S. pneumoniae*.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

Doripenem displays antibacterial activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria. The spectrum of activity includes staphylococci, streptococci, *Enterobacteriaceae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, *Acinetobacter* spp., *Bordetella* spp., *Bacteroides* spp., *Prevotella* spp, *Clostridium* spp., and other Gram-positive anaerobes. MIC90s for these species were usually < 1 µg/ml. Doripenem was less active against methicillin-resistant *S. aureus* (MRSA), *Enterococcus faecalis*, and was inactive against most isolates of *Enterococcus faecium*, *Corynebacterium* spp. and *Stenotrophomonas maltophilia*.

Doripenem was less active than imipenem but more active than meropenem and ertapenem against Gram-positive bacteria. Against Gram-negative bacteria, the activity of doripenem was comparable to meropenem and comparable or more active than imipenem and ertapenem. The metabolite of doripenem, M1, was tested *in vitro* and shown to be microbiologically inactive.

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Doripenem exhibits time-dependent bactericidal activity against common pathogens such as *S. aureus*, *S. pneumoniae*, *P. aeruginosa* and *Enterobacteriaceae*. Activity, as exhibited by MIC value, was relatively unaffected by changes in medium, pH or serum.

Gram-Positive Organisms

Table 3 shows the *in vitro* susceptibility for a variety of Gram-positive bacteria.

More than 800 isolates of *Streptococcus pneumoniae* were tested. While penicillin-susceptible *S. pneumoniae* (PSSP) isolates were susceptible to doripenem with MIC90 values ≤ 0.06 $\mu\text{g/ml}$, penicillin-intermediate and -resistant isolates of *S. pneumoniae* demonstrated MIC90s for doripenem of 0.25—0.5 $\mu\text{g/ml}$ and 0.5—1 $\mu\text{g/ml}$, respectively.

Other non-*S. pneumoniae* isolates of streptococci had a MIC90 value of 0.06 $\mu\text{g/ml}$. For *S. milleri*, *S. constellatus* and *S. intermedius*, doripenem had a MIC90 = 0.12 $\mu\text{g/ml}$ (p. 24, current submission). *S. pyogenes* were susceptible to doripenem, with MIC90 values ≤ 0.02 $\mu\text{g/ml}$. *S. agalactiae* isolates had MIC90 values of 0.15—0.06 $\mu\text{g/ml}$.

Activity of doripenem against the staphylococci varied with methicillin susceptibility. Among methicillin-susceptible *S. aureus*, doripenem exhibited MIC90 values ≤ 0.1 $\mu\text{g/ml}$. However, among methicillin-resistant *S. aureus*, doripenem exhibited MIC90 values ≥ 16 $\mu\text{g/ml}$. Among methicillin-susceptible *S. epidermidis*, doripenem displayed MIC 90 values of 0.03—0.06 $\mu\text{g/ml}$ in two studies while in a third study, these isolates displayed a MIC90 = 12.5 $\mu\text{g/ml}$. Yet, against methicillin-resistant *S. epidermidis* isolates, susceptibilities to doripenem were 4, 32 and 50 $\mu\text{g/ml}$. In *S. haemolyticus*, doripenem had a MIC90 value of 0.8 $\mu\text{g/ml}$ against methicillin-susceptible isolates. However, for methicillin-resistant isolates, doripenem was poorly active (MIC90 value of 100 $\mu\text{g/ml}$).

Doripenem displayed activity against *Enterococcus faecalis* with MIC90 values of 4—16 $\mu\text{g/ml}$. Note that susceptibilities for *E. faecalis* demonstrated a wide range of MICs. Against *E. faecium*, *E. avium* and *Enterococcus* spp, doripenem was not active with MIC90 values > 32 $\mu\text{g/ml}$.

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Table 3. *In Vitro* Susceptibility of Gram-Positive Facultative Bacteria

Species	N	Range	MIC (µg/ml)		Applicant Reference	
			MIC50	MIC90		
<i>Staphylococcus epidermidis</i> , methicillin-susceptible	39	≤0.015--0.06	0.03	0.03	3	
	54	0.025--50	0.1	12.5	24	
	46	0.03--0.12	0.03	0.06	25	
	methicillin-resistant	17	≤0.015--4	1	4	3
		54	0.8-->100	25	50	24
	27	8--32	16	32	25	
<i>Staphylococcus haemolyticus</i> methicillin-susceptible	54	0.05--1.6	0.4	0.8	24	
	54	0.8--100	6.2	100	24	
<i>Staphylococcus saprophyticus</i>	0					
<i>Streptococcus intermedius</i>	0					
<i>Streptococcus constellatus</i>	0					
<i>Streptococcus agalactiae</i>	132	0.016--0.03	0.016	0.03	25, 26	
	40	≤0.013--0.025	0.025	0.025	24	
	33	0.039--0.25	0.08	0.06	27	
macrolide-susceptible	20	≤0.008--0.015	0.015	0.015	3	
macrolide-resistant	20	0.015--0.03	0.015	0.015	3	
<i>Streptococcus pneumoniae</i> penicillin-susceptible	118	≤0.015	≤0.015	≤0.015	22, 26	
	44	≤0.008	≤0.008	≤0.008	3	
	16	≤0.03--0.06	≤0.03	0.06	23	
	25	0.004--0.016	0.008	0.008	25	
	penicillin-intermediate	10	≤0.015--0.5	0.03	0.25	22
		23	0.015--0.5	0.12	0.25	3
	penicillin-resistant	83	0.016--0.5	0.06	0.5	26
		23	0.25--2	0.5	1	22
		122	0.25--2	0.5	1	3, 26
		10	≤0.03--1	0.25	0.5	23
	25	0.016--2	0.25	0.5	25	
ceftriaxone-resistant	11	0.5--2	0.5	1	2	
macrolide-resistant	20	0.016--1	0.25	1	26	
<i>Streptococcus pyogenes</i>	100	0.016--0.06	0.016	0.016	26	
	42	≤0.004	≤0.004	≤0.004	25	
macrolide-susceptible	10	≤0.008	≤0.008	≤0.008	3	
<i>Enterococcus avium</i>	37	0.2-->100	25	100	24	
<i>Enterococcus faecalis</i>	45	≤0.015-->32	4	16	22	
	20	1--8	4	8	3	
	132	0.5-->32	2	8	26	
	54	1.6--25	6.2	12.5	24	
	26	0.5--16	2	4	25	

Source: Appendix 1.1, Clinical Microbiology Studies, this submission.

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Table 4. *In Vitro* Susceptibility of Gram-negative Facultative Bacteria.

Species	N	Range	MIC (µg/ml)		Applicant Reference	
			MIC50	MIC90		
<i>Escherichia coli</i>	22	<0.015-0.06	0.03	0.03	3	
	30	0.016-0.25	0.03	0.03	21	
	31	<0.015-0.03	<0.015	<0.015	22	
	54	0.025-0.2	0.05	0.1	24	
	31	0.0078-1	0.06	0.25	27	
	20	<0.03-0.06	<0.03	<0.03	23	
	30	0.016-0.03	0.016	0.03	25	
	10	<0.015-0.03	<0.015	0.03	28	
	beta-lactamase positive	17	<0.008-0.5	0.03	0.12	35
	ESBL	29	<0.015-0.12	<0.015	0.03	2
	18	<0.015-0.06	0.03	0.06	3	
	20	0.016-0.12	0.03	0.03	21	
<i>Klebsiella oxytoca</i>	10	<0.03-0.12	0.06	0.06	34	
	20	0.03-0.12	0.03	0.06	3	
	20	<0.015-0.06	0.03	0.06	22	
	27	0.05-0.8	0.1	0.1	24	
	38	0.03-0.06	0.06	0.06	25	
	(K1 hyperproducers)	21	<0.03-0.25	0.06	0.06	34
	(ESBL positive)	3	0.06	0.06	ND	21
<i>Klebsiella pneumoniae</i>	20	0.03-0.25	0.03	0.12	3	
	10	<0.015-0.06	0.03	0.06	28	
	26	<0.015-0.06	0.03	0.03	22	
	31	0.03-1	0.06	0.12	21	
	54	0.05-0.4	0.1	0.2	24	
	20	<0.03-0.25	0.06	0.12	23	
	30	0.03-0.12	0.03	0.06	25	
	(ESBL)	34	<0.015-0.25	0.03	0.06	2
		20	<0.015-0.25	0.06	0.12	3
	<i>Klebsiella spp.</i>	50	<0.03-0.25	0.06	0.12	34
<i>Proteus mirabilis</i>	23	0.03-0.12	0.06	0.12	22	
	22	0.12-2	0.5	1	3	
	15	0.06-1	0.25	1	21	
	54	0.4-0.8	0.4	0.8	24	
	27	0.06-1	0.25	0.5	25	
	10	0.12-0.5	0.25	0.5	28	
	(ESBL)	11	0.06-0.25	0.12	0.25	2
		19	0.25-2	1	2	3
<i>Salmonella spp.</i>	23	<0.015-0.12	0.03	0.06	22	
	19	0.03-0.25	0.06	0.12	21	
<i>Citrobacter diversus</i>	25	0.016-0.06	0.03	0.03	21	
<i>Citrobacter freundii</i>	25	0.03-0.06	0.03	0.03	21	
	54	0.025-0.8	0.1	0.4	24	
	22	0.03-0.12	0.03	0.06	25	
	(ceftazidime-susceptible)	21	<0.015-0.06	0.03	0.03	3

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(ceftazidime-nonsusceptible)	20	0.03-0.25	0.06	0.12	3
<i>Enterobacter aerogenes</i>	54	0.025-6.2	0.2	0.4	24
(ceflazidime-susceptible)	23	0.03-0.12	0.06	0.12	3
(ceflazidime-nonsusceptible)	20	0.06-0.12	0.12	0.12	3
<i>Enterobacter cloacae</i>	54	0.05-6.2	0.4	3.1	24
	20	<0.03-0.25	0.06	0.25	23
	30	0.03-0.12	0.03	0.06	25
(ceflazidime-susceptible)	10	<0.015-0.06	0.03	0.06	28
	23	0.03-0.12	0.03	0.06	3
	24	0.03-0.06	0.03	0.06	21
(ceftazidime-nonsusceptible)	19	0.06-0.25	0.12	0.25	3
(AmpC-derepressed)	21	0.06-0.5	0.06	0.12	34
(AmpC-inducible)	10	<0.03-0.06	0.06	0.06	34
<i>Morganella morganii</i>	20	0.06-0.5	0.25	0.5	3
	10	0.25-1	0.5	0.5	21
	54	0.2-1.6	0.8	0.8	24
	32	0.06-0.5	0.12	0.25	25
<i>Proteus mirabilis</i>	23	0.03-0.12	0.06	0.12	22
	22	0.12-2	0.5	1	3
	15	0.06-1	0.25	1	21
	54	0.4-0.8	0.4	0.8	24
	27	0.06-1	0.25	0.5	25
(ESBL)	10	0.12-0.5	0.25	0.5	28
	11	0.06-0.25	0.12	0.25	2
	19	0.25-2	1	2	3
<i>Proteus vulgaris</i>	12	0.25-2	0.5	0.5	21
	37	0.2-0.8	0.4	0.8	24
	30	0.06-0.5	0.25	0.5	25
<i>Providencia rettgeri</i>	10	0.12-0.5	0.25	0.5	21
	54	0.1-100	0.4	1.6	24
	21	0.06-1	0.12	0.25	25
<i>Providencia stuartii</i>	5	0.12-0.5	ND	ND	21
<i>Serratia marcescens</i>	24	0.03-0.5	0.25	0.5	21
	21	0.06-0.5	0.12	0.25	3
	24	0.03-0.5	0.06	0.12	22
	54	0.1->100	0.8	6.2	24
	20	0.06-0.25	0.12	0.12	23
	30	0.06-4	0.12	0.25	25
(ceftazidime-nonsusceptible)	10	0.03-2	0.12	0.5	2
	19	0.12-0.25	0.12	0.25	3
(carbapenem-resistant)	2	0.25-4	0.25	ND	2
<i>Shigella</i> spp.	22	<0.015-0.06	0.03	0.03	22
	20	0.03-0.06	0.03	0.06	21
<i>Haemophilus influenzae</i>	20	0.06-2	0.12	1	23
	50	0.03-1	0.12	0.5	25
(beta-lactamase +)	28	0.12-1	0.12	0.5	22
	150	<0.016-1	0.12	0.25	26

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(beta-lactamase -)	99	<0.016-2	0.12	0.5	26
	33	<0.015-1	0.12	1	22
	10	<0.015-0.5	0.12	0.25	28
(beta-lactamase-negative, ampicillin-resistant--BLNAR)	5	4-Feb	2	ND	2
(beta-lactamase-negative, ampicillin-nonsusceptible)	49	<0.016-4	0.5	2	26
(carbapenem-resistant)	10	0.12-1	0.5	0.5	2
<i>Acinetobacter baumannii</i>	33	0.03->32	0.5	16	22
(ceftazidime-susceptible)	10	0.06-1	0.12	1	28
	20	0.12-1	0.25	1	3
(ceftazidime-nonsusceptible)	10	0.25->16	1	>16	3
<i>Acinetobacter calcoaceticus</i>	42	0.2-100	0.8	3.1	24
<i>Pseudomonas aeruginosa</i>	35	0.06-1	0.25	0.5	22
	150	0.03-16	0.25	1	21
	78	0.25-16	0.25	1	29
	54	0.05-0.25	0.8	12.5	24
	20	0.06-4	0.12	1	23
(CF-isolates)	82	0.25-256	0.25	2	29
(CF-isolates) mucoid	200	0.25-512	8	32	33
(CF-isolates) non-mucoid	200	0.25-512	8	64	33
(beta-lactamase-positive)	15	0.5-8	2	4	30
(ceftazidime-resistant)	39	0.06-16	2	8	25
(carbapenem-sensitive)	83	0.06-8	0.25	2	25
(carbapenem-resistant)	32	16-Feb	8	8	25
	34	0.5->32	8	>32	2
(ciprofloxacin-resistant)	16	0.12-8	0.5	8	25
(gentamicin-resistant)	37	0.06-16	0.5	8	25
(metallo-beta-lactamases)	15	4->32	>32	>32	2
	15	4->64	64	64	30

Source: Appendices 1.2 and 1.3, Clinical Microbiology Studies, this submission.

Gram-Negative Facultative Bacteria (Excluding Non-Fermenters)

Both *Salmonella* spp. and *Shigella* spp. demonstrated low doripenem MIC₉₀ values. MIC₉₀ values of 0.06—0.12 µg/ml were observed among *Salmonella* isolates. MIC₉₀ values of 0.03—0.06 µg/ml were observed among *Shigella*.

Doripenem MIC₉₀ values of ≤ 0.12 µg/ml were demonstrated by *Citrobacter* spp., *Escherichia coli* (including those with ESBL or other β-lactamases), *K. oxytoca* (including those harboring ESBL and K1 hyperproducers), *K. pneumoniae* and other *Klebsiella* spp. (with and without ESBL).

Doripenem was active against several species of *Enterobacter*. In most studies, *E. aerogenes* (both ceftazidime-susceptible and ceftazidime-resistant), *E. cloacae* and *Enterobacter* spp. (ceftazidime-susceptible, ceftazidime-resistant, AmpC- inducible and AmpC-derepressed), demonstrated MIC₉₀ values ≤ 0.25 µg/ml.

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With the exception of one study, *Serratia marcescens* demonstrated doripenem MICs \leq 0.5 $\mu\text{g/ml}$. Against doripenem, *Morganella morganii*, *Proteus mirabilis*, *P. vulgaris*, and *P. rettgeri* demonstrated MIC90 values \leq 1 $\mu\text{g/ml}$. Against most *Haemophilus influenzae* (including β -lactamase positive) isolates, doripenem MIC90 values were \leq 1 $\mu\text{g/ml}$. The exception were β -lactamase negative, ampicillin-nonsusceptible isolates which demonstrated MIC90s = 2 $\mu\text{g/ml}$.

It is interesting to note that several species from a particular study had higher MIC90 values than species from other studies.

Non-Fermentative Gram-Negative Bacteria

Extensive testing of *Pseudomonas aeruginosa* (>1100 isolates) including cystic fibrosis (CF) isolates was conducted. The majority of doripenem MIC90 values were \leq 1—2 $\mu\text{g/ml}$. Isolates that were β -lactamase positive, ceftazidime-resistant, carbapenem-resistant, ciprofloxacin-resistant and gentamicin resistant demonstrated doripenem MIC90 values of 4—8 $\mu\text{g/ml}$. Against multidrug-resistant *P. aeruginosa* CF isolates, doripenem displayed an elevated MIC90 value of 32 $\mu\text{g/ml}$ (mucoïd isolates) or 64 $\mu\text{g/ml}$ (non-mucoïd isolates). *P. aeruginosa* with metallo- β -lactamases demonstrated doripenem MIC90 values of > 64 $\mu\text{g/ml}$.

Acinetobacter baumannii (ceftazidime-susceptible) and *Acinetobacter calcoaceticus* demonstrated MIC90 values of 1 $\mu\text{g/ml}$ and 3.1 $\mu\text{g/ml}$, respectively. MIC90 values for carbapenem-resistant and ceftazidime-nonsusceptible isolates of *A. baumannii* were \geq 16 $\mu\text{g/ml}$.

The Applicant has included doripenem susceptibility data for a number of organisms that were not included in this review including:

[Handwritten scribbles]

As these organisms are not pertinent to the indication, these data are not shown.

Reviewer's comments: The Applicant has requested that the following Gram-negative facultative bacteria be included on the *in vitro* list of the Microbiology Section of the Package Insert:

- *[Handwritten scribble]*
- *[Handwritten scribble]*
- *Citrobacter freundii* *[Handwritten scribble]*
- *Enterobacter aerogenes* *[Handwritten scribble]*
- *Enterobacter cloacae* *[Handwritten scribble]*
- *[Handwritten scribble]*

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- / / / / / /
-
- *Morganella morganii*,
- / /
-
-
-
-
- *Serratia marcescens* _____
- _____

However, the following organisms from the *in vitro* list cannot be granted

- / / / / / /

following organisms may be granted

- Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*

- / / / / / /
- and *Serratia marcescens* (

_____ are not pertinent to the indication and should not be granted.

This Reviewer deems the following aerobic and facultative Gram-negative organisms to be appropriate for inclusion in the second list of the Package Insert:

- *Citrobacter freundii*
- *Enterobacter cloacae*
- / /
- *Klebsiella oxytoca*
- *Morganella morganii*
- _____ and
- *Serratia marcescens*.

Anaerobes

Table 5 shows the *in vitro* doripenem susceptibility data for a variety of anaerobic bacteria.

Doripenem MIC90 values were $\leq 1 \mu\text{g/ml}$ for *Peptostreptococcus magnus*, *Propionibacterium* spp., *Bacteroides ovatus*, *B. thetaiotaomicron*, most other *Bacteroides*

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SURVEILLANCE STUDIES

Approximately 17,000 organisms each year for three years (2003—05) were tested through a global surveillance program. Isolates were collected from a variety of body sites. The geographic distribution of sites covered three regions: North America, Latin America and Europe with approximately 20 sites per region. Tables 6, 7 and 8 present surveillance data from North America, Europe and Latin America, respectively.

Table 6. Doripenem Susceptibility Surveillance Data from North America

Organism	MIC (µg/ml)					
	2003		2004		2005	
	MIC90	Range	MIC90	Range	MIC90	Range
<i>S. aureus</i> (all)	ND	ND	ND	ND	8	≤0.06-->8
<i>S. aureus</i> (MSSA)	≤0.06	0.016-->16	0.06	0.016--0.5	≤0.06	≤0.06--2
<i>S. aureus</i> (MRSA)	ND	ND	ND	ND	>8	≤0.06-->8
CoNS (all)	ND	ND	ND	ND	8	≤0.06-->8
CoNS (oxacillin S)	0.06	0.016--4	0.06	≤0.008--2	≤0.06	≤0.06--0.12
CoNS (oxacillin R)	ND	ND	ND	ND	>8	≤0.06-->8
<i>E. faecalis</i>	8	0.016-->16	8	0.5-->16	8	≤0.06-->8
<i>E. faecium</i>	ND	ND	>16	0.016-->16	>8	≤0.06-->8
β-haemolytic streptococci	0.03	≤0.008--0.12	0.03	≤0.008--0.12	≤0.06	≤0.06--0.12
<i>S. pneumoniae</i>	1	≤0.008--1	0.5	≤0.008--2	0.5	≤0.06--1
Viridans streptococci	0.25	≤0.008--2	0.5	≤0.008--1	0.12	≤0.06--1
<i>E. coli</i>	0.03	≤0.008--0.25	0.03	≤0.008--4	≤0.06	≤0.06--0.25
<i>Klebsiella</i> spp.	0.06	0.016-->16	0.06	0.016-->16	≤0.06	≤0.06-->8
<i>Enterobacter</i> spp.	0.12	≤0.008--4	0.12	0.016--2	0.12	≤0.06-->8
<i>E. cloacae</i>	ND	ND	0.12	0.016--1	0.12	≤0.06-->8
<i>Citrobacter</i> spp.	0.06	0.016--2	0.06	0.016--1	≤0.06	≤0.06--0.12
<i>P. mirabilis</i>	0.25	0.016--0.5	0.25	0.03--2	0.25	≤0.06--1
<i>Serratia</i> spp.	0.25	0.03--1	0.25	0.03-->16	0.25	≤0.06--8
<i>Salmonella</i> spp.	0.12	0.016--0.25	0.12	0.03--0.25	0.12	≤0.06--0.12
<i>P. aeruginosa</i>	2	0.06-->16	4	0.016--16	4	≤0.06-->8
<i>Acinetobacter</i> spp.	2	0.06-->16	4	0.016--16	4	≤0.06-->8
<i>H. influenzae</i>	0.25	≤0.008--1	0.5	≤0.008--2	0.5	≤0.06--0.5

Source: Appendix 2.1, Microbiology Section, this submission.

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Table 7. Doripenem Susceptibility Surveillance Data from Europe

Organism	MIC ($\mu\text{g/ml}$)					
	2003		2004		2005	
	MIC90	Range	MIC90	Range	MIC90	Range
<i>S. aureus</i> (all)	ND	ND	ND	ND	8	≤ 0.06 -->8
<i>S. aureus</i> (MSSA)	0.06	0.016-->16	0.06	0.016--2	≤ 0.06	≤ 0.06 --1
<i>S. aureus</i> (MRSA)	ND	ND	ND	ND	>8	≤ 0.06 -->8
CoNS (all)	ND	ND	ND	ND	8	≤ 0.06 -->8
CoNS (oxacillin S)	0.06	≤ 0.008 --8	0.06	0.016-->16	≤ 0.06	≤ 0.06 --0.5
CoNS (oxacillin R)	ND	ND	ND	ND	>8	≤ 0.06 -->8
<i>E. faecalis</i>	8	≤ 0.008 -->16	8	0.03-->16	8	≤ 0.06 -->8
<i>E. faecium</i>	ND	ND	>16	1-->16	>8	≤ 0.06 -->8
β -haemolytic streptococci	0.03	≤ 0.008 --1	0.5	≤ 0.008 --2	0.5	≤ 0.06 --1
<i>S. pneumoniae</i>	0.5	≤ 0.008 --1	0.5	≤ 0.008 --2	0.5	≤ 0.06 --1
Viridans streptococci	0.5	≤ 0.008 -->16	1	≤ 0.008 --4	0.25	≤ 0.06 -->8
<i>E. coli</i>	0.03	≤ 0.008 --1	0.03	≤ 0.008 --0.25	≤ 0.06	≤ 0.06 --0.5
<i>Klebsiella</i> spp.	0.06	0.016-->16	0.06	0.016--16	0.12	≤ 0.06 -->8
<i>Enterobacter</i> spp.	0.12	0.016--4	0.25	0.016--16	0.12	≤ 0.06 -->8
<i>E. cloacae</i>	ND	ND	0.25	0.016--16	0.25	≤ 0.06 -->8
<i>Citrobacter</i> spp.	0.06	≤ 0.008 --0.12	0.12	0.03--1	≤ 0.06	≤ 0.06 --2
<i>P. mirabilis</i>	0.25	0.03--0.5	0.25	0.03--1	0.25	≤ 0.06 -->8
<i>Serratia</i> spp.	0.25	0.03--0.05	0.25	0.06-->16	0.25	≤ 0.06 --0.5
<i>Salmonella</i> spp.	0.06	0.03--0.25	0.06	0.016--0.12	≤ 0.06	≤ 0.06 --0.12
<i>Shigella</i> spp.	0.06	0.016--0.06	ND	ND	ND	ND
<i>P. aeruginosa</i>	8	0.03-->16	16	0.03-->16	8	≤ 0.06 -->8
<i>Acinetobacter</i> spp.	8	0.016--16	16	0.03-->16	8	≤ 0.06 -->8
<i>Aeromonas</i> spp.	2	0.03--4	ND	ND	ND	ND
<i>H. influenzae</i>	0.25	≤ 0.008 --2	0.5	≤ 0.008 --1	0.25	≤ 0.06 --0.5

Source: Appendix 2.2, Microbiology Section, this submission.

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Table 8. Doripenem Susceptibility Surveillance Data from Latin America

Organism	MIC (µg/ml)					
	2003		2004		2005	
	MIC90	Range	MIC90	Range	MIC90	Range
<i>S. aureus</i> (all)	ND	ND	ND	ND	>8	≤0.06-->8
<i>S. aureus</i> (MSSA)	0.06	≤0.008-->16	0.06	≤0.008--2	≤0.06	≤0.06--0.5
<i>S. aureus</i> (MRSA)	ND	ND	ND	ND	>8	≤0.06-->8
CoNS (all)	ND	ND	ND	ND	>8	≤0.06-->8
CoNS (oxacillin S)	0.12	0.016--2	0.12	≤0.008--1	≤0.06	≤0.06--0.12
CoNS (oxacillin R)	ND	ND	ND	ND	>8	≤0.06-->8
<i>E. faecalis</i>	>16	≤0.008-->16	>16	0.016-->16	>8	0.5-->8
<i>E. faecium</i>	ND	ND	>16	0.03-->16	>8	≤0.06-->8
β-haemolytic streptococci	0.03	≤0.008--0.06	0.03	≤0.008--0.03	≤0.06	≤0.06
<i>S. pneumoniae</i>	0.5	≤0.008--1	0.5	≤0.008--2	0.5	≤0.06--0.5
Viridans streptococci	2	≤0.008--4	NA	0.016--0.12	1	≤0.06--2
<i>E. coli</i>	0.06	0.016--0.25	0.03	≤0.008--0.5	≤0.06	≤0.06--1
<i>Klebsiella</i> spp.	0.06	0.016--0.25	0.03	≤0.008--0.5	≤0.06	≤0.06--1
<i>Enterobacter</i> spp.	0.25	0.016--1	0.25	0.03--1	0.25	≤0.06--4
<i>E. cloacae</i>	ND	ND	0.25	0.03--1	0.25	≤0.06--4
<i>Citrobacter</i> spp.	0.06	0.016--0.06	0.06	0.03--0.25	0.12	≤0.06--1
<i>P. mirabilis</i>	0.25	0.03--0.5	0.25	0.016--0.5	0.25	≤0.06--0.5
<i>Serratia</i> spp.	0.25	0.03--0.5	0.25	0.03--4	0.25	≤0.06--0.25
<i>Salmonella</i> spp.	0.12	0.03--0.25	0.06	0.016--0.6	≤0.06	≤0.06--0.12
<i>Shigella</i> spp.	0.03	0.03--0.06	ND	ND	ND	ND
<i>P. aeruginosa</i>	8	0.03-->16	16	0.06-->16	8	<0.06-->8
<i>Acinetobacter</i> spp.	4	0.12-->16	8	0.03-->16	>8	<0.06-->8
<i>Aeromonas</i> spp.	ND	ND	ND	ND	ND	ND
<i>H. influenzae</i>	0.25	0.016--2	0.25	0.016--2	≤0.06	≤0.06--0.12

Source: Appendix 2.3, Microbiology Section, this submission.

The following summarizes doripenem's activity against staphylococci, enterococci, streptococci, *Enterobacteriaceae* and non-fermenters,

Doripenem susceptibility tends to follow oxacillin susceptibility among the staphylococci. For oxacillin-susceptible *S. aureus*, the doripenem MIC90s for all three geographic regions were ≤ 0.06 µg/ml for each of the three surveillance years. No increase in maximal MICs were observed over the three years that included >2000 *S. aureus* isolates per year. Oxacillin-resistant staphylococci, which are not within the spectrum of doripenem, were only tested in 2005 and the MIC90 for doripenem was > 8 µg/ml for all three geographic regions.

For oxacillin-susceptible coagulase-negative staphylococci (CoNS) for each of the three surveillance years, the MIC90s for North America, Europe and Latin America for doripenem was ≤ 0.06 µg/ml. Oxacillin-resistant CoNS, which are not within the

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spectrum of doripenem, were only tested in 2005 and the MIC₉₀ was > 8 µg/ml for all three geographic regions.

The enterococci were less susceptible to doripenem than other Gram-positive cocci. *E. faecalis* collections containing less than 10% non-*E. faecium* enterococci showed slightly variable susceptibilities based on geographic region. The MIC₉₀ for doripenem for North America and Europe was 8 µg/ml for each of the three surveillance years, whereas in Latin America, the MIC₉₀ for doripenem ranged from > 8 µg/ml to > 16 µg/ml over the three surveillance years. As *E. faecium* isolates are not considered to be within the spectrum of doripenem, there was no testing done against *E. faecium* in 2003, and a limited number of isolates was tested in 2004-5. Testing conducted across all three geographic regions showed a doripenem MIC₉₀ of > 8 µg/ml for 2004 and a MIC₉₀ > 16 µg/ml for 2005.

There was variation in MIC₉₀ values among the different streptococci. Among the β-hemolytic streptococci from North America and Latin America, the MIC₉₀ for doripenem was 0.03 µg/ml for 2003 and 2004 and ≤ 0.06 µg/ml for 2005. However, the MIC₉₀s in Europe increased from 0.03 to 0.5 µg/ml for 2003 and 2004/2005 respectively. Against all *S. pneumoniae*, including penicillin-resistant pneumococci, doripenem MIC₉₀ values were 0.5 µg/ml and in one case, 2003 in North America, MIC₉₀ = 1 µg/ml; no trend was discerned when MIC ranges were compared across the three year period. Against viridans group streptococci including penicillin-resistant isolates, doripenem MIC₉₀ values were 0.12 to 0.5 µg/ml in North America; 0.25 to 1 µg/ml in Europe; and 1 to 2 µg/ml for small numbers of isolates in Latin America.

Generally, low doripenem MIC values were observed for *Enterobacteriaceae*. Doripenem MIC₉₀ values for *E. coli* ranged from 0.03–0.06 µg/ml or were ≤ 0.06 µg/ml for all three geographic regions. Doripenem MIC₉₀ values for *Klebsiella* spp. ranged from 0.03 to 0.12 µg/ml in all three geographic regions. In *Citrobacter* spp., doripenem MIC₉₀ values were generally 0.06 µg/ml in all three regions for all three years with the exception of Latin America, 2005 (0.12 µg/ml). The doripenem MIC₉₀ values for *P. mirabilis* were 0.25 µg/ml for all three geographic regions for all three years.

MIC values were generally higher for the non-fermenters. In North America, MIC₉₀ values for *P. aeruginosa* ranged from 2 to 4 µg/ml during the three-year study period. In Europe and Latin America, MIC₉₀ values ranged from 8 to 16 µg/ml. In North America, MIC₉₀ values for *Acinetobacter* spp. ranged from 2 to 4 µg/ml during the three-year study period. Doripenem MIC₉₀ values ranged from 8 to 16 µg/ml and from 4 to > 8 µg/ml in Europe and Latin America, respectively.

Reviewer's comments: Surveillance studies of doripenem susceptibility among clinical isolates were conducted during 2003–2005 in three different geographical regions: North America, Europe and Latin America. In general, MIC₉₀s remained

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constant or increased by one dilution step over the three years of the surveillance studies for all the organisms surveyed.

However, while MIC90s remained unchanged, there was more variability in MICs from year to year due to increases in the upper end of the MIC ranges for each organism. Oxacillin-susceptible staphylococci and *H. influenzae* demonstrated MIC decreases in the upper end of the MIC ranges over the three year study for all three regions. The increases in the upper end of the MIC ranges tended to occur among the *Enterobacteriaceae*. This was most apparent in isolates from Latin America where increases occurred with isolates of *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *E. cloacae* and *Citrobacter* spp. Increases in MICs were seen among *Enterobacter* spp., *E. cloacae* and *Serratia* spp. isolates from North America. Increases in MICs were seen among *Citrobacter* spp. and *P. mirabilis* isolates from Europe. While these increases in the upper end of the MIC ranges were not MIC90s, these increases may signal potential increases in MIC90s and may warrant monitoring over time.

ANTIMICROBIAL INTERACTIONS

Antimicrobial chemotherapy for serious infections may require combination therapy. Co-administration of antibiotics can affect the relative efficacy of the individual agents, with each antibiotic acting synergistically, additively, indifferently or antagonistically. In two separate *in vitro* checkerboard studies combinations of doripenem and glycopeptides were synergistic or additive with tested clinical MRSA isolates. In a second study that evaluated additional Gram-positive and Gram-negative species, doripenem's activity was generally additive with each of the compounds tested: amikacin, levofloxacin, cotrimoxazole, daptomycin, linezolid and vancomycin, for the various species tested.

Synergy

Synergistic activity was evaluated for doripenem and other carbapenems with various comparators using the checkerboard technique in two separate studies. In the first study, doripenem, and the comparators imipenem, panipenem and meropenem were coadministered with the glycopeptides vancomycin and teicoplanin against 27 clinical MRSA blood isolates; all isolates were imipenem resistant. The media used for checkerboard testing was Mueller Hinton agar. Synergy was evaluated according to the respective fractional inhibitory concentration or FIC, calculated from (MIC doripenem combined/MIC doripenem alone) + (MIC glycopeptides combined/MIC glycopeptides alone). A FIC < 0.5 was considered synergistic, FIC values between 0.5 and 1 were superadditive, equal to 1 additive, FIC values between 1 and 2 were indifferent, and FIC values > 2 were antagonistic. Results are summarized in Table 9.

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Table 9. Evaluation of Synergy between Carbapenems and Glycopeptides in 27 Clinical MRSA Isolates

Drug Combination		Number of Strains ^a				
		Synergistic	Super-additive	Additive	Indifferent	Antagonistic
Vancomycin	Doripenem	21	5	0	1	0
	Imipenem	23	4	0	0	0
	Panipenem	21	5	0	1	0
	Meropenem	20	6	0	1	0
Teicoplanin	Doripenem	25	1	0	1	0
	Imipenem	26	1	0	0	0
	Panipenem	26	0	0	1	0
	Meropenem	26	0	0	1	0

^aA total of 27 strains was tested.

Source: Table 30, this submission.

Synergy with doripenem and vancomycin or teicoplanin was detected in at least 74% of the isolates; with one exception, the remaining isolates were superadditive. Note that these definitions do not correspond with current nomenclature adopted by American and European microbiologists who recognize only the terms Synergistic, Indifference and Antagonism.

In the second study, using a checkerboard protocol, doripenem was compared to vancomycin, daptomycin, levofloxacin or linezolid against MSSA, MRSA, *S. pneumoniae* or *E. faecalis* (vancomycin-susceptible); and with amikacin, levofloxacin or trimethoprim-sulfamethoxazole against *E. coli*, *E. cloacae*, *K. pneumoniae*, *A. baumannii* or *P. aeruginosa*. The media used for checkerboard testing was Mueller Hinton agar with the exception of daptomycin testing which was on IsoSensitest agar with 50 mg/L calcium. Results were considered synergistic or additive if SFIC values were < 1, indifferent with values between 1 and 2, and antagonistic for SFIC values > 2. Results are summarized Table 10 below.

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Table 10. Summary of Σ FIC Values for Antibiotic Combinations with Doripenem by Species

Organism	Geometric mean Σ FIC			
	Amikacin	Levofloxacin	Co-trimoxazole ^a	
Enterobacteriaceae (17) ^b	0.87	0.96	0.99	
<i>A. baumannii</i> (5)	0.79	0.97	0.81	
<i>P. aeruginosa</i> (14)	0.65	0.85	1.29	
Agar without blood	Daptomycin	Levofloxacin	Linezolid	Vancomycin
<i>E. faecalis</i> (6)	0.59	0.54	0.71	0.62
MRSA(5)	0.48	0.57	0.60	0.86
MSSA(6)	0.86	0.86	0.96	0.90
Agar with blood	Daptomycin	Levofloxacin	Linezolid	Vancomycin
<i>E. faecalis</i> (6)	0.53	0.71	0.91	0.94
MRSA(5)	0.59	0.50	0.70	0.75
MSSA(6)	0.84	0.67	0.86	0.92
<i>S. pneumoniae</i> (11)	0.93	0.83	0.90	0.79

^atrimethoprim-sulfamethoxazole

^bNumber of strains

Source: Table 31, this submission.

Against Gram-negative species tested, the doripenem-antibiotic combinations were generally additive, with most geometric mean Σ FIC values falling between 0.7 and 1. With *P. aeruginosa*, the combination of doripenem and co-trimoxazole (trimethoprim-sulfamethoxazole) was indifferent, with individual Σ FIC up to 3.0 indicating cases of weak antagonism; this probably resulted from the inherently poor activity of co-trimoxazole against *P. aeruginosa*, and from the recognized difficulty in obtaining accurate MIC values for this compound with *P. aeruginosa*.

Against Gram-positive species, doripenem-antibiotic combination effects were either additive (Σ FIC values between 0.7 and 1) or weakly synergistic (Σ FIC values proximal to 0.5). In this study, the combination of doripenem and daptomycin was weakly synergistic with *E. faecalis* or MRSA; but additive with MSSA and *S. pneumoniae*.

Reviewer's comments: Two studies demonstrated that doripenem could be combined with a range of antimicrobials without risk of antagonism, suggesting that coadministration with other agents would not lead to loss of activity. Doripenem was synergistic when combined with vancomycin or teicoplanin against MRSA. In another study, doripenem was synergistic when combined with amikacin, levofloxacin or co-trimoxazole against *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii*. In the same study, doripenem was also synergistic when combined with daptomycin, levofloxacin, linezolid or vancomycin against MSSA, MRSA, *Enterococcus faecalis* and *S. pneumoniae*.

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BACTERICIDAL ACTIVITY

Carbapenem antibiotics, like other β -lactams, exhibit time-dependent bactericidal activity. Bactericidal activity is considered an important attribute in treating acute life-threatening infections. In several studies described below doripenem was shown to be bactericidal to various degrees against key clinical pathogens including *S. aureus*, *E. coli*, *P. aeruginosa*, *E. faecalis*, *S. pneumoniae*, *K. pneumoniae* and *E. cloacae*.

MBC Evaluations

In one study evaluating doripenem and comparators against 20 *S. aureus*, *E. coli* and *P. aeruginosa* isolates, doripenem maintained consistent bactericidal activity against the *S. aureus* and *E. coli* isolates tested, with MBC90 and MIC90 values of 0.12 and 0.06 $\mu\text{g/ml}$, respectively, against both isolates (Table 11). Against *P. aeruginosa*, doripenem MBC90 and MIC90 values were approximately 2-fold lower than those of meropenem and imipenem. The MBC90 to MIC90 ratios of either of the carbapenems were 2 for the *S. aureus*, *E. coli* and *P. aeruginosa* isolates tested, suggesting potent bactericidal activity against these organisms.

Table 11. Bactericidal Activities of Doripenem against *S. aureus*, *E. coli* and *P. aeruginosa* Clinical Isolates

Isolate	N	MIC90 ($\mu\text{g/ml}$)	MBC90 ($\mu\text{g/ml}$)	MBC90/ MIC90
<i>S. aureus</i>	20	0.06	0.12	2
<i>E. coli</i>	20	0.06	0.12	2
<i>P. aeruginosa</i>	20	1	2	2

Source: Table 8, this submission.

In a separate study measuring the MBC and MIC values of doripenem against 10 individual Gram-positive and Gram-negative isolates (Table 12), MBC/MIC ratios of 8 were observed against four single isolates of *A. baumannii*, *E. cloacae*, *E. coli* and *P. aeruginosa*; the remaining six isolates (*E. coli*, *K. pneumoniae*, *E. faecalis*, *S. aureus*, *S. pneumoniae*) had MBC/MIC ratios of 2 or 4.

Table 12. Bactericidal Activities of Doripenem against Ten Gram-Positive and Gram-Negative Isolates

Isolate	MIC90 ($\mu\text{g/ml}$)	MBC90 ($\mu\text{g/ml}$)	MBC90/ MIC90
<i>A. baumannii</i>	0.5	4	8
<i>E. cloacae</i>	0.25	2	8
<i>E. coli</i>	0.015	0.12	8
<i>E. coli</i>	0.03	0.06	2
<i>K. pneumoniae</i>	0.06	0.25	4
<i>P. aeruginosa</i>	0.25	2	8
<i>E. faecalis</i>	2	8	4
<i>S. aureus</i>	0.03	0.12	4
<i>S. aureus</i>	0.03	0.12	4

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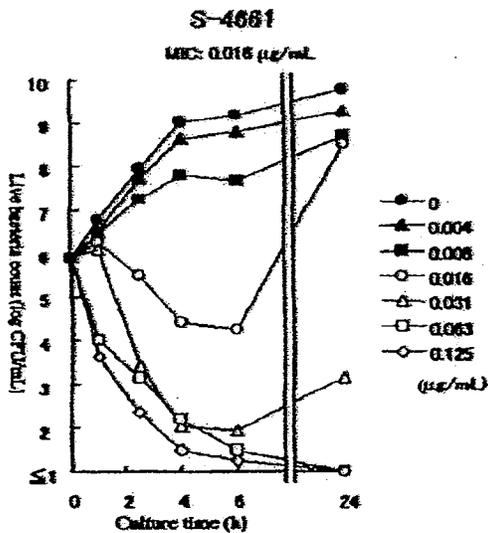
S. pneumoniae 0.03 0.12 4
Source: Table 9, this submission.

Time-Kill Studies

Time-kill experiments designed to demonstrate that doripenem is bactericidal. In a study summarized in Figures 1—3, doripenem was evaluated at multiples of the MIC against three isolates, *S. aureus* Smith, *E. coli* NIHJ JC-2 and *P. aeruginosa* ATCC 27853.

Against *S. aureus* Smith, doripenem was bactericidal at 2-, 4- and 8-times the MIC, decreasing the log₁₀ CFU values approximately 3-orders of magnitude or more within the first 2 h; by 24 h, at 4- and 8-times the MIC, values remained at or below 10 CFU per ml, a decrease of approximately 5 log₁₀. At 2-times the doripenem MIC, some regrowth was noted by 24 h, although bacterial counts remained at approximately 10³ CFU/ml, a 3-log decrease from the initial concentration of 10⁶ CFU/ml.

Figure 1. Bactericidal Activity of Doripenem (S-4661) against *S. aureus* Smith



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Note: *S. aureus* Smith MIC = 0.016 µg/ml
Source: Figure 1, this submission.

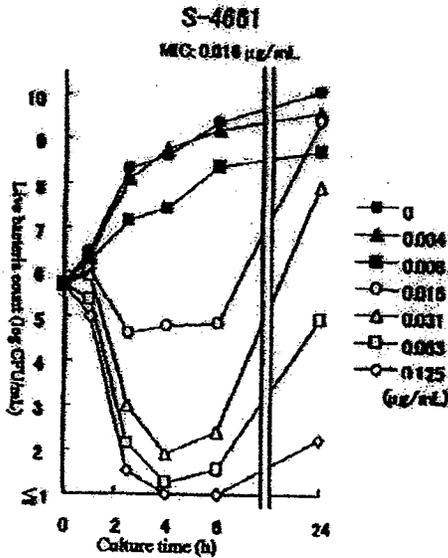
Doripenem exhibited similar rates of bactericidal activity against the *E. coli* isolate, with CFU values decreasing by approximately 10³ CFU/ml within the first 2 h post exposure at 2-, 4- and 8-times the MIC; and CFU values decreasing by approximately 10⁴ CFU/ml or more after 4 h; by 24 h regrowth at all concentrations was observed (Figure 2).

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Figure 2. Bactericidal Activity of Doripenem (S-4661) against *E. coli* NIHJ JC-2

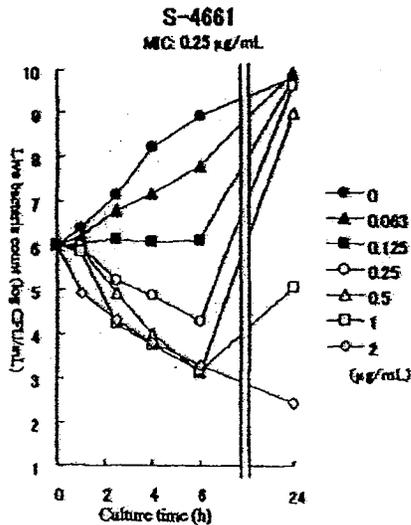


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Note: *E. coli* NIHJ JC-2 MIC = 0.016 µg/ml;
 Source: Figure 2, this submission.

In time-kill experiments performed with *P. aeruginosa* ATCC 27853, doripenem was bactericidal after 6 h, with CFU values decreasing by approximately 3 log₁₀ values at 2-, 4- and 8-times the MIC (Figure 3). By 24 h, regrowth of the 2-times and 4-times MIC cultures was noted. At 8-times the MIC, doripenem was bactericidal over 24 h with this isolate, reducing the CFU value by approximately 3.5 log₁₀.

Figure 3. Bactericidal Activity of Doripenem (S-4661) against *P. aeruginosa* ATCC 27853



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Note: *P. aeruginosa* ATCC 27853 MIC = 0.25 µg/ml
Source: Figure 3, this submission.

In a general comparison of doripenem at 2-, 4- or 8-times the MIC against the *S. aureus*, *E. coli* or *P. aeruginosa* isolates, the rate of bactericidal activity of doripenem was similar and was not concentration dependent, consistent with the time-dependent efficacy of β -lactam antibiotics.

In a second time kill study, doripenem was evaluated against five *P. aeruginosa* isolates at 2-, 4- and 8-times the MIC. At 2-times the MIC, doripenem was bactericidal (>3 log₁₀ decrease in CFU/ml) at 6 h and 24 h with 3 of 5, and 1 of 5 isolates, respectively. At 4-times the MIC, doripenem was bactericidal at 6 h and 24 h with 3 of 5 and 3 of 5 isolates, respectively. At 8- times the MIC, doripenem was bactericidal at 6 h and 24 h with 4 of 5 and 4 of 5 isolates, respectively. Importantly, doripenem decreased the CFU/ml by at least 2 log₁₀ for all isolates, at all concentrations tested at 6 and 24 h, with the following exceptions: at 4-times the MIC, one isolate exhibited a 1.6-fold reduction in log₁₀ CFU/ml at 24 h, and at 2-times the doripenem MIC, there was regrowth with two *P. aeruginosa* isolates by 24 h achieving CFU/ml above initial inoculum levels.

In a third time-kill study, 10 Gram-negative and Gram-positive isolates were evaluated at 2-, 4- and 8-times the doripenem MIC. Table 13 summarizes these results.

Table 13. Bactericidal Activity against Various Gram-positive and Gram-negative Bacteria

Organism	Isolate	6 Hours			24 Hours		
		MIC 2X	(µg/ml) 4X	8X	MIC 2X	(µg/ml) 4X	8X
<i>S. aureus</i>	Smith	√	√	√	√	√	√
<i>S. aureus</i>	ATCC 25923		√*	√*		√	√
<i>S. aureus</i>	ATCC 29213	√*	√*	√*		√	√
<i>E. faecalis</i>						√	√
<i>S. pneumoniae</i>		√*	√*	√*	√	√	√
<i>E. coli</i>	NIHJ JC-2	√	√	√			√
<i>E. coli</i>	ATCC 35218			√*	√	√	√
<i>E. coli</i>	ATCC 25922		√*	√*			√
<i>K. pneumoniae</i>	43-4591C	√*	√*	√*		√	√
<i>E. cloacae</i>	46-273D		√*	√*			√
<i>P. aeruginosa</i>	ATCC 27853	√	√	√			√
<i>P. aeruginosa</i>		√	√	√	√	√	√
<i>P. aeruginosa</i>		√	√	√		√	√
<i>P. aeruginosa</i>		√	√	√		√	√
<i>P. aeruginosa</i>				√			√
<i>P. aeruginosa</i>				√			√
<i>P. aeruginosa</i>	ATCC 27853		√*	√*			√
<i>A. baumannii</i>				√*			√

*Cells treated for 8 hours.

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Against two *S. aureus* isolates (ATCC 25923 and ATCC 29213), doripenem was bactericidal at 4- or 8-times the MIC at 8 and 24 h, and at 2-times the MIC with ATCC 29213 at 8 h. Against *E. faecalis*, doripenem was bactericidal after 24 h at 4- or 8-times the MIC: at 2-, 4- or 8-times the MIC at 8 h, CFU values had decreased by 2, 2.5 and 2.5 log₁₀, respectively. Against *S. pneumoniae*, doripenem was bactericidal at all concentrations tested, at 8 h and at 24 h (4.3 and 6 log₁₀ decreases on CFUs/ml respectively). Against *E. coli* ATCC 35218, doripenem was bactericidal at 8-times the MIC at 8 h, and at all concentrations at 24 h: at 2- and 4-times the MIC, the 8 h log₁₀ CFU/ml values decreased by almost 3 log₁₀. Against *E. coli* ATCC 25922, doripenem was bactericidal at 4- and 8-times the MIC at 8 h, and at 8-times the MIC at 24 h. Against *K. pneumoniae* 43-4591C, doripenem was bactericidal at all concentrations at 8 h, and at 4- and 8-times the MIC at 24 h. Against *E. cloacae* 46-273D, doripenem was bactericidal at 4- and 8-times the MIC at 8 h, and at 8-times the MIC at 24 h. Against *P. aeruginosa* ATCC 27853, doripenem was bactericidal at 4- and 8-times the MIC at 8 h and at 8-times the MIC at 24 h. Against *A. baumannii*, doripenem was bactericidal at 8-times the MIC at 8 and 24 h.

Reviewer's comments: Carbapenem antibiotics, like other β -lactams, exhibit time-dependent bactericidal activity. Bactericidal activity is considered an important attribute in treating acute life-threatening infections. The Applicant presents both MBC and time-kill studies to assess the bactericidal activity of doripenem. In several studies described here, conflicting data are presented regarding bactericidal activity of doripenem.

The Applicant presents data from three time-kill studies for 18 bacterial isolates (8 different species). Table 13 lists the bactericidal activities (defined as a 3 log₁₀ reduction in CFU/ml) of these isolates.

The greatest bactericidal activity was seen against the Gram-positive isolates, *S. aureus* and *S. pneumoniae* with the exception of *E. faecalis* to which doripenem was bactericidal over long (24 hours) but not short periods of time (8 hours).

Doripenem demonstrated the least amount of bactericidal activity against the Gram-negatives e.g. *Enterobacteriaceae* (*E. coli*, *K. pneumoniae* and *E. cloacae*) particularly the non-fermenters (*P. aeruginosa* and *A. baumannii*). *The reduced bactericidal activity against the Enterobacteriaceae and non-fermentative Gram-negatives are of concern as these are key pathogens in the indications sought i.e. cUTI and cIAI.*

POSTANTIBIOTIC EFFECTS***In Vitro***

Doripenem was shown to exhibit *in vitro* a species-dependent PAE. As shown in Table 14, a moderate *in vitro* PAE (1.8-1.9 h) was observed against *S. aureus* and *P. aeruginosa*. As with other carbapenems, the PAE was typically short against species such as *E. coli* and *K. pneumoniae* (less than 1 h).

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Table 14. *In Vitro* Postantibiotic Effect of Doripenem

Strains ^a	Doripenem	Imipenem	Panipenem	Ceftazidime
<i>S. aureus</i> Smith	1.9	1.6	1.8	1.8
<i>K. pneumoniae</i> BK	0.3	0.5	0.4	0.1
<i>E. coli</i> ATCC 25922	0.5	0.6	0.6	0.4
<i>P. aeruginosa</i> ATCC 27853	1.8	1.0	1.0	-0.3

^aTested at 4 X MIC for 2 h

Source: Table 27, this submission.

However, an additional study on *P. aeruginosa* E2 demonstrated a relatively short *in vitro* PAE versus *P. aeruginosa* (0.8 h). In this study, the PAE for meropenem and imipenem were also relatively short at 1.1 and 1.5 h respectively, and thus, similar.

***In Vivo*—Neutropenic Mouse Thigh Model**

In a neutropenic mouse model thigh infection, doripenem was shown to demonstrate a bacterial species dependent PAE. In this model, neutropenia was induced by injecting cyclophosphamide i.p. on days 4 and 1 before infection. Doripenem, imipenem-cilastatin, or panipenem-betamipron (50 mg/kg or 100 mg/kg), were injected s.c. 2 h after inoculating the organism into both thighs. The time when the viable cell number returned to the starting inoculum level was defined as the effective regrowth time. The PAE for doripenem ranged from 7.8 to 8.0 h for *S. aureus* and *P. aeruginosa*, to 5 h for *K. pneumoniae* (Table 15).

Table 15. *In Vivo* PAE of Doripenem in a Murine Neutropenic Mouse Thigh Infection

Strains	Doripenem	Imipenem	Panipenem	Ceftazidime
<i>S. aureus</i> Smith	7.8	12.3	10.8	ND ^a
<i>K. pneumoniae</i> BK	5.0	5.5	4.3	6.0
<i>P. aeruginosa</i> ATCC 27853	8.0	9.8	8.3	2.7

a=Not determined

Source: Table 28, this submission.

***In Vivo*—Mouse Respiratory Infection Model**

PAE was calculated by determining the time difference between the control and the treated groups for the bacteria in the lungs to grow 10-fold compared to the time at which the serum concentration of drug fell below its MIC for *P. aeruginosa* E-2. PAEs of doripenem, meropenem-cilastatin, imipenem-cilastatin, and ceftazidime are found in Table 16. Doripenem had a similar PAE to the other carbapenems tested (but not ceftazidime) in this neutropenic respiratory infection model.

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Table 16. *In Vivo* PAE of Doripenem in a Murine Neutropenic Respiratory Infection Model Caused by *P. aeruginosa*

Organism (CFU/mouse)	Compound ^a	MIC (µg/ml)	PAE (reliability limit, h)
<i>P. aeruginosa</i> E-2, CAZ-R (1.1 x 10 ⁷)	Doripenem	1	6.12 (3.15-9.08)
	Meropenem	1	5.90 (3.12-8.67)
	Imipenem	0.5	3.49 (1.40-5.58)
	Ceftazidime	4	0.35 ^b

^aSingle dose, 2.5 h after infection

^bNo limits were obtained because the PAE was almost absent

Source: Table 29, this submission.

Reviewer's comments: Doripenem exhibits a species-dependent postantibiotic effect (PAE) both *in vitro* and *in vivo*. *In vitro*, a moderate PAE (1.9 to 2 h) was observed against *S. aureus* and *P. aeruginosa*. As with other carbapenems, the PAE was typically short against species such as *E. coli* and *K. pneumoniae* (less than 1 h). In an additional study, the *in vitro* PAE versus *P. aeruginosa* was relatively short (0.8 h) but was roughly comparable to meropenem (1.1 h).

In contrast, a prolonged PAE was shown *in vivo* in two animal models. In a neutropenic mouse thigh model, doripenem exhibited a PAE that ranged from 7.8 to 8.0 h for *S. aureus* and *P. aeruginosa* to 5 h for *K. pneumoniae*. In a neutropenic mouse respiratory infection model, the PAE of doripenem against a ceftazidime-resistant *P. aeruginosa* was greater than 6 h.

LPS EFFECTS

The antimicrobial efficacy and lipopolysaccharide (LPS) release following treatment with doripenem, meropenem-cilastatin, imipenem-cilastatin, and ceftazidime was evaluated in a neutropenic rat model of bloodstream infection. Sprague-Dawley rats were rendered neutropenic by injections of cyclophosphamide four days and one day prior to infection. Rats were infected i.p. with *P. aeruginosa* SR24 and then treated one h after infection with 50 mg/kg of lead tetraacetate to enhance the LPS effect. Two hours after infection, rats were given 30 mg/kg doripenem, meropenem-cilastatin, imipenem-cilastatin, or 50 mg/kg of ceftazidime subcutaneously. Rats were euthanized, the numbers of *P. aeruginosa* SR24 were determined from the blood, and LPS release was assayed from the serum.

The log₁₀ reduction of CFU/ml in the blood of rats infected with *P. aeruginosa* SR24 for all of the treatments was similar except for the ceftazidime at 1 h where the reduction was only 0.2 log₁₀ CFU/ml from the control. Doripenem, meropenem-cilastatin, and imipenem-cilastatin treatment resulted in a 1.4 log₁₀ CFU/ml at the 1-h time point. At 3 and 6 h all treatments achieved > 3 and > 4 log₁₀ CFU/ml reduction from the control respectively.

There was a significant difference ($P < 0.05$) in serum LPS release between the control rats and the carbapenems treated rats at the 1-h time point. The non-significance of ceftazidime vs. control group may be due to the decrease killing of *P. aeruginosa* by

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ceftazidime at 1 h in this assay. Doripenem caused the lowest serum LPS concentration of any of the carbapenems tested at 1 and 3 h.

Reviewer's comments: The antimicrobial efficacy and lipopolysaccharide (LPS) release following treatment with doripenem, meropenem-cilastatin, imipenem-cilastatin, and ceftazidime was evaluated in a neutropenic rat model of bloodstream infection. Doripenem produced the lowest serum LPS concentration of any of the carbapenems tested at 1 and 3 h.

MECHANISMS OF RESISTANCE

The predominant mechanism of resistance to carbapenems in Gram-positive bacteria is reduced affinity for altered penicillin binding proteins (PBPs). The presence of carbapenemases, AmpC cephalosporinase overexpression, and altered permeability and efflux are the predominant mechanisms of carbapenem resistance in Gram-negative bacteria.

The most common mechanism described for carbapenem resistance in *P. aeruginosa* is the loss or reduced expression of the outer membrane protein OprD55, frequently coupled with the β -lactamase-mediated resistance related to the upregulation of the chromosomal AmpC, found in as many as 72% of imipenem-resistant *P. aeruginosa* isolates.

Reduced susceptibility associated with elevated levels of AmpC, in combination with porin loss, has also been described in *K. pneumoniae*, *E. cloacae* and *Proteus rettgeri*. In *K. pneumoniae*, an increase in the Class A carbapenemases of the KPC family has also occurred in the past few years, initially in the New York City area, but spreading to other regions in the US and other countries. In the US, isolates expressing metallo- β -lactamases are extremely rare at this time, but production of these enzymes varies considerably worldwide.

Similar resistance mechanisms have been reported for doripenem although mechanisms conferring resistance to imipenem or meropenem do not necessarily confer the same degree of resistance to doripenem.

In studies of resistance frequency in *P. aeruginosa*, doripenem selected for resistant mutants less frequently than imipenem and meropenem. Doripenem-resistant mutants, like those selected with other carbapenems, often lacked the OprD outer membrane protein.

 β -Lactamase-Mediated Resistance to Doripenem

Stability to β -lactamases is one of the key determinants of potency and spectrum of activity of β -lactam antibiotics. Enzyme-mediated drug degradation, as well as the binding and sequestration of drug by these enzymes, results in reduced susceptibility of β -lactamase-bearing isolates. The stability of doripenem and comparators to β -lactamases

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of molecular classes A-D was determined. Doripenem, like meropenem and imipenem, was stable to plasmid- or chromosome-mediated β -lactamases of Classes A, C, and D.

When tested with the Class B metallo- β -lactamases, doripenem was readily hydrolyzed by the chromosomal Class B carbapenemase produced by *S. maltophilia* and the plasmid-encoded enzyme IMP-1 produced by *E. coli*.

For the *S. maltophilia* L1 chromosomal metallo- β -lactamase, doripenem hydrolysis was similar to other carbapenems. The K_m value for doripenem was low, indicating high affinity binding to the enzyme. The relative (V_{max}/K_m) value was similar to the comparator cephalothin, indicating efficient hydrolysis by this β -lactamase. The stability of doripenem and comparators to hydrolysis by the SME-3 and KPC-2 Class A carbapenemases was studied. The K_m value for doripenem was approximately 25 times lower than that for imipenem, indicating a higher binding affinity for doripenem compared to imipenem. The low K_m value for doripenem resulted in a hydrolytic efficiency similar to those for imipenem and meropenem.

The CTX-M family of extended-spectrum β -lactamases (ESBLs) is a rapidly-expanding class of β -lactamases that are found in *Enterobacteriaceae* worldwide. Hydrolysis of the carbapenems was extremely slow with this enzyme. The hydrolytic efficiency for doripenem was approximately 25,000-fold less than for the readily hydrolyzed comparator substrate, cephaloridine. Doripenem and the comparator carbapenems were very stable to hydrolysis by the AmpC enzyme of *E. cloacae*, P99.

Susceptibility Profiles in Characterized β -Lactamase-Producing Isolates

The results of the β -lactamase hydrolysis studies correlate well with the examination of MIC values for bacterial isolates containing known β -lactamases. The activity of doripenem and comparators against molecularly characterized β -lactamase-producing isolates was determined. Doripenem maintained its activity against most β -lactamase-producing bacteria. The majority of organisms with class A, C, and D enzymes had MIC values $< 0.5 \mu\text{g/ml}$. *Enterobacteriaceae* that constitutively produce AmpC cephalosporinases also had doripenem MIC values $< 0.5 \mu\text{g/ml}$.

The activity of doripenem and comparators against *K. pneumoniae* and *E. coli* isolates expressing the CTX-M-15, CTX-M-10 and CTX-M-3-like ESBLs were studied using CLSI broth or agar methodology. Doripenem MIC values were $< 0.06 \mu\text{g/ml}$ for the *E. coli* isolates and $< 0.12 \mu\text{g/ml}$ for *K. pneumoniae*, indicating that doripenem retains potent activity against CTX-M-expressing isolates. In a set of four *P. aeruginosa* clinical isolates producing PER-1 ESBL, the doripenem MIC values ranged from 2-4 $\mu\text{g/mL}$, compared to 4-8 $\mu\text{g/mL}$ meropenem and 16 $\mu\text{g/mL}$ for imipenem.

Isolates of *P. aeruginosa*, *Klebsiella* spp., and *Serratia marcescens* that produced Class A carbapenemases or Class-B metallo- β -lactamases had notably reduced susceptibility to doripenem, with MIC values for isolates expressing these enzymes that ranged from 4 to

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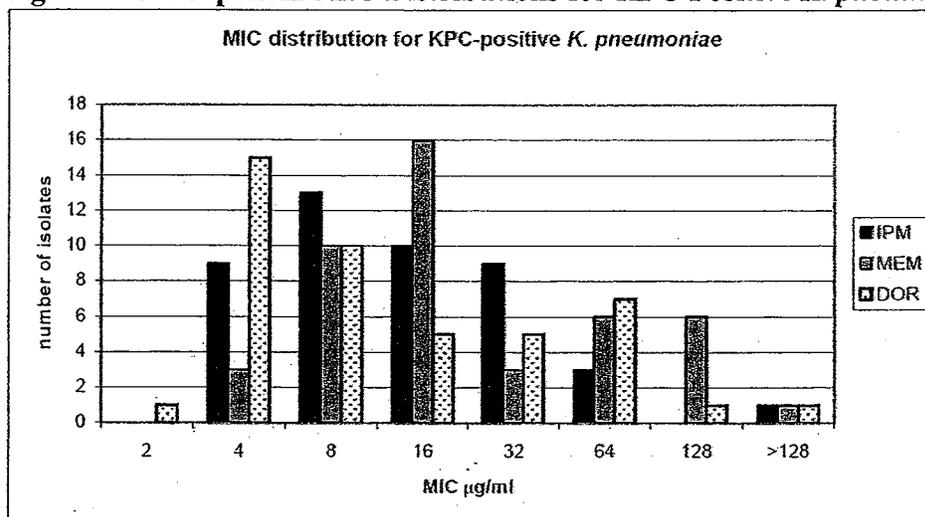
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> 64 µg/ml. These data indicate that doripenem is rendered ineffective by the Class B metallo-β-lactamases such as VIM and IMP, and the class A carbapenemases. In addition, *Acinetobacter* spp. with Class D oxacillin-hydrolyzing (OXA) β-lactamases such as OXA-23 had reduced susceptibility to doripenem.

KPC-carbapenemases, a group of plasmid-encoded enzymes reported in clinical isolates in the United States, and recently detected throughout the world, were investigated in further detail. The doripenem, imipenem and meropenem MIC distributions for 45 clinical isolates producing KPC enzymes are shown in Figure 4. In this study, doripenem MIC₅₀ (8 µg/ml) and MIC₉₀ (64 µg/ml) values were similar or one dilution lower than those obtained for imipenem and one dilution lower than meropenem. The range of MIC values observed was 2 µg/ml to >128 µg/ml for doripenem, and 4 µg/ml to >128 µg/ml for imipenem and meropenem.

AmpC overproduction in the absence of other resistance mechanisms resulted in doripenem, meropenem and imipenem MIC values of 0.5 to 2 µg/ml, considered to be in the susceptible range. In contrast, AmpC overproduction combined with loss of OprD in *P. aeruginosa* resulted in carbapenem MIC values of 8 to 16 µg/ml.

Figure 4. Carbapenem MIC Distributions for KPC Positive *K. pneumoniae* Isolates



Source: Figure 4, 04 June 2007 submission.

Decreased Outer Membrane Permeability and Active Efflux

Outer membrane permeability and efflux mechanisms have been most extensively studied in *P. aeruginosa*. It has been reported that doripenem is a substrate for the MexAB-OprM, MexCD-OprJ and MexXY-OprM multidrug efflux pumps of *P. aeruginosa*. A recent survey of the frequency of 450 *P. aeruginosa* isolates chosen for reduced susceptibility to ticarcillin reported overexpression of the MexAB system and MexXY in 46% and 58% of the isolates, respectively. Carbapenem MICs, however, were not evaluated in this set of isolates. Another common carbapenem resistance mechanism

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involves the outer membrane protein OprD, the major porin that allows carbapenem entry into the cell that is frequently mutated as a first step in the development of resistance. The loss of OprD differentially affects susceptibility to various carbapenems, with imipenem affected to the greatest extent.

In the *Enterobacteriaceae*, in general, a combination of resistance mechanisms is required to result in carbapenem resistance. The combination of porin loss and AmpC overexpression has been associated with carbapenem resistance. Examination of imipenem-resistant clinical isolates of *K. pneumoniae* revealed loss of an outer membrane porin and high levels of the AmpC β -lactamase ACT-1 that resulted in resistance to imipenem. In *A. baumannii*, loss of an outer membrane protein, CarO, is also known to result in resistance to imipenem and meropenem. In *B. fragilis*, multiple passage on doripenem selected resistant mutants that overexpressed the *bmeB1* and *bmeB11* efflux pumps 3.8- and 4.4-fold, respectively. The MIC values for doripenem rose from 0.13 to 16 $\mu\text{g/ml}$ over the course of this selection.

Resistance Selection *In Vitro*

Resistance selection by imipenem commonly produces mutants with high levels of AmpC β -lactamase production and/or alterations in permeability and efflux. OprD-negative mutants of *P. aeruginosa* have been selected at a frequency of 10^{-7} when exposed to imipenem.

Two studies documented the *in vitro* selection of resistance to doripenem *P. aeruginosa*. In both of these studies, doripenem-resistant mutants were selected at frequencies lower than either imipenem or meropenem. In a population analysis experiment designed to measure the frequency of carbapenem-resistant mutants, cultures of ten *P. aeruginosa* clinical isolates were plated on agar with concentrations of doripenem, meropenem and imipenem at one-half the MIC. A subset of the colonies that grew at this concentration was examined for carbapenem resistance. For the samples plated on meropenem and imipenem, resistant colonies were obtained, but no resistant colonies were obtained in samples plated on doripenem. Resistance frequencies for this set of *P. aeruginosa* isolates plated at 1.5 to 16X the MIC were $< 2 \times 10^{-9}$ for doripenem, 1.4×10^{-8} to 1.1×10^{-7} for meropenem and 2.9×10^{-9} to 1.2×10^{-8} for imipenem. Resistant mutants were obtained when the *P. aeruginosa* isolates were incubated overnight in broth cultures containing up to 2X MIC for doripenem, 4X MIC for imipenem and 16X MIC for meropenem. In these experiments, doripenem-resistant mutants, as well as those selected with imipenem and meropenem, had a loss of a 48KDa outer membrane protein, presumably OprD, when compared to the parent isolate.

One serial passage study examined the increase in doripenem MIC values using a set of six *P. aeruginosa* isolates (baseline doripenem MIC values 2-8 $\mu\text{g/mL}$) plated on doripenem alone or doripenem combined with gentamicin. In this study, selection with doripenem led to MIC increases that were >8 -fold in three isolates, 2-fold in one isolate and were unchanged in two isolates. Selection with doripenem and gentamicin resulted in

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one isolate with a 4-fold doripenem MIC increase, two isolates with a 2-fold increase and three isolates with unchanged MIC values.

The single-step resistance characteristics for a set of eight *P. aeruginosa* isolates were determined for doripenem, imipenem and meropenem. For doripenem, three isolates produced resistant mutants at 2X MIC, one isolate produced resistant mutants at 4X MIC and no resistant mutants were selected at 4X and 8X MIC. The resistance frequency at 4X and 8X MIC based on the number of CFU plated was approximately $< 2 \times 10^{-9}$. When tested with imipenem, six isolates produced mutants at 2X MIC, two isolates produced mutants at 4X MIC and resistant mutants were selected from three isolates at 8X MIC. For meropenem, seven isolates produced mutants at 2X and 4X MIC, and three isolates produced mutants at 8X MIC. At 16X MIC, no mutants were selected with meropenem or imipenem.

In multiple-step mutant selection, doripenem MIC values rose from 0.5 to 32 $\mu\text{g/ml}$ by the fifth selection cycle. Imipenem and meropenem MIC values also reached 32 $\mu\text{g/ml}$ and 64 $\mu\text{g/ml}$, respectively by the fifth passage. Doripenem-resistant colonies also appeared in fewer isolates than mutants selected with ertapenem, carbenicillin, ceftazidime, ciprofloxacin and tobramycin. When the outer membrane proteins from a subset of the single step mutants selected with doripenem were examined, each lacked the OprD protein. One isolate with a doripenem MIC value of 32 $\mu\text{g/ml}$ selected by multiple passage also had a five-fold increase in (AmpC) β -lactamase activity.

A serial passage experiment in the presence of doripenem, imipenem and meropenem was performed with single *S. aureus*, *E. coli* and *P. aeruginosa* isolates to determine the maximum MIC values achievable for each compound (Tables 17—19).

Table 17. *S. aureus* Smith Multiple Passage Study

Passage #	DOR			MEM			IPM		
	MIC	Passage ($\mu\text{g/ml}$)		MIC	Passage ($\mu\text{g/ml}$)		MIC	Passage ($\mu\text{g/ml}$)	
	DOR	MEM	IPM	DOR	MEM	IPM	DOR	MEM	IPM
1	0.02	0.06	0.02	0.02	0.06	0.02	0.02	0.06	0.02
4	0.03	0.12	0.02	0.03	0.06	0.02	0.03	0.06	0.02
8	0.06	0.12	0.02	0.12	0.25	0.03	0.06	0.12	0.02
12	0.5	1	0.12	0.5	2	0.25	0.06	0.25	0.03
14	1	2	0.25	0.5	2	0.25	0.12	0.25	0.03

DOR= doripenem, MEM=meropenem, IPM=imipenem
Source: Table 17, this submission.

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Table 18. *E. coli* NIHJ JC-2 Multiple Passage Study

Passage #	DOR			MEM			IPM		
	MIC	Passage (µg/ml)		MIC	Passage (µg/ml)		MIC	Passage (µg/ml)	
	DOR	MEM	IPM	DOR	MEM	IPM	DOR	MEM	IPM
1	0.03	0.02	0.12	0.03	0.02	0.12	0.03	0.02	0.12
4	0.03	0.03	0.25	0.06	0.06	0.25	0.06	0.06	0.25
8	0.06	0.06	0.25	1	2	0.25	0.12	0.06	0.5
12	0.25	0.06	1	1	2	0.5	0.12	0.06	1
14	0.25	0.06	1	2	4	0.5	0.12	0.06	1

DOR= doripenem, MEM=meropenem, IPM=imipenem
Source: Table 18, this submission.

Table 19. *P. aeruginosa* ATCC 25619 Multiple Passage Study

Passage #	DOR			MEM			IPM		
	MIC	Passage (µg/ml)		MIC	Passage (µg/ml)		MIC	Passage (µg/ml)	
	DOR	MEM	IPM	DOR	MEM	IPM	DOR	MEM	IPM
1	0.06	0.03	0.5	0.06	0.03	0.5	0.06	0.03	0.5
4	0.25	0.25	0.5	1	0.25	16	0.12	0.12	1
8	4	2	8	4	4	16	2	2	16
12	4	4	16	4	8	16	2	2	16
14	4	4	16	4	8	16	4	4	16

DOR= doripenem, MEM=meropenem, IPM=imipenem
Source: Table 19, this submission.

As shown in Tables 17-19, the MIC values increased for all isolates upon incubation with increasing concentrations of each agent. In *S. aureus*, the highest doripenem MIC attainable was 1 µg/ml, for meropenem it was 2 µg/ml and for imipenem, it was 0.25 µg/ml. In *E. coli*, the highest doripenem MIC attainable was 2 µg/ml, for meropenem it was 4 µg/ml and for imipenem, it was 1 µg/ml. In *P. aeruginosa*, the highest doripenem MIC attainable was 4 µg/ml, for meropenem it was 8 µg/ml and for imipenem, it was 16 µg/ml. Mechanisms of resistance were not evaluated in this study.

Alteration of Target Sites- PBP Mutations

In the Gram-positive bacteria, resistance to β-lactams is often due to the expression of alternate penicillin binding proteins that are refractory to the inhibitory binding of the β-lactam. In methicillin-resistant *S. aureus* (MRSA), PBP 2a (the enzyme product of the acquired *mecA* gene) completes the process in cell wall synthesis normally carried out by the inhibited PBPs. The PBP 2a protein is inhibited by doripenem with an IC50 of 250 µg/ml. As expected, methicillin-resistant *S. aureus*, expressing the PBP 2a protein, has a doripenem MIC90 value of 16 µg/ml. In penicillin-resistant *S. pneumoniae*, the modified PBP 2x has reduced affinity to doripenem, meropenem and imipenem (see Table 2). However, although the activity of doripenem against PRSP is reduced, the MIC90 value against PRSP remains 1 µg/ml.

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Reviewer's comments: In *K. pneumoniae*, an increase in the Class A carbapenemases of the KPC family has also occurred in the past few years, initially in the New York City area, but spreading to other regions in the US and other countries. Doripenem MICs for these isolates ranged from 2 µg/ml to > 128 µg/ml. This MIC range should be of concern and is much higher than the MIC90 = 0.06 µg/ml seen in surveillance studies. This Reviewer recommends that in the future, all *K. pneumoniae* isolates be screened for the presence of the KPC carbapenemases.

The Applicant presents the results of a serial passage study that examined the increase in doripenem MIC values using a set of six *P. aeruginosa* isolates (baseline doripenem MIC values 2-8 µg/mL) plated on doripenem alone or doripenem combined with gentamicin. In this study, selection with doripenem led to MIC increases that were >8-fold in three isolates, 2-fold in one isolate and were unchanged in two isolates. Selection with doripenem and gentamicin resulted in one isolate with a 4-fold doripenem MIC increase, two isolates with a 2-fold increase and three isolates with unchanged MIC values.

The Applicant presents the results of multiple passage studies on one isolate each of *S. aureus*, *E. coli* and *P. aeruginosa* as indicated by changes in MICs presented in Tables 17—19. The results indicate Doripenem MICs increased by 6, 3 and 6 dilution steps when passaged in *S. aureus*, *E. coli* and *P. aeruginosa*, respectively.

The results of the serial passage study and the multiple passage studies with *P. aeruginosa* are a cause for concern that resistance may develop in future clinical isolates.

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PRECLINICAL EFFICACY—*IN VIVO*

ANIMAL EFFICACY STUDIES

Acute infections Due to Gram-Positive Bacteria

Systemic infections were established by infecting ICR mice i.p. with a lethal Gram-positive pathogen. In all studies reported here, an equimolar concentration of cilastatin was added to meropenem and imipenem. Subcutaneous treatment with doripenem, meropenem-cilastatin, imipenem-cilastatin, ceftazidime, or vancomycin was given after infection. Mice were treated with one or two doses and observed for seven days and the ED50 (the effective dose that protected 50% of the mice from death) values were calculated from the survival rates. These ED50 values are listed in Table 20.

Table 20. Efficacy of Doripenem against Gram-Positive Organisms in the Mouse Peritonitis Model

Organism (CFU/mouse)	Antibiotic	MIC ($\mu\text{g/ml}$)	Dosing Frequency	ED50 (95% CI) (mg/kg/dose)
<i>S. aureus</i> Smith (2.4×10^6)	Doripenem	0.02	bid*	0.04 (0.03--0.06)
	Meropenem	0.06		0.19 (0.05--0.71)
	Imipenem	0.02		0.02 (0.01--0.03)
	Ceftazidime	8		3.83 (1.03--14.3)
<i>S. aureus</i> Smith (1.1×10^6)	Doripenem	0.032	qd**	0.066 (0.032--0.17)
	Meropenem	0.06		0.41 (0.24--0.94)
	Imipenem	0.02		0.05 (0.03--0.14)
	Ceftazidime	8		14.7 (7.3--47.9)
<i>S. aureus</i> TUHI-MRSA (5.5×10^7)	Doripenem	4	qd**	19.2 (11.9--31.3)
	Meropenem	16		48.4 (28.0--132)
	Imipenem	16		34.5 (18.2--88.0)
	Vancomycin	1		3.1 (2.01--4.45)
<i>S. pneumoniae</i> type 1 (1.2×10^3)	Doripenem	0.008	bid*	0.35 (0.22--0.56)
	Meropenem	0.008		0.71 (0.41--1.21)
	Imipenem	0.008		0.10 (0.06--0.16)
	Ceftazidime	0.12		11.3 (5.66--22.7)
<i>S. pneumoniae</i> SR 16754 (PRSP) (1.2×10^6)	Doripenem	0.25	bid*	1.41 (1.06--1.89)
	Meropenem	0.25		2.24 (1.79--2.81)
	Imipenem	0.12		0.81 (0.62--1.05)
	Ceftazidime	8		28.5 (22.8--35.7)
<i>S. pyogenes</i> C-203 (1.4×10^2)	Doripenem	0.008	bid*	0.02 (0.021--0.022)
	Meropenem	0.008		0.09 (ND) †
	Imipenem	0.008		0.02 (0.021--0.022)
	Ceftazidime	0.06		0.22 (0.21--0.22)
<i>E. faecalis</i> SR1004 (3.8×10^3)	Doripenem	2	bid*	6.26 (4.35--9.0)
	Meropenem	4		7.56 (5.26--10.9)
	Imipenem	0.5		0.69 (0.47--1.01)
	Ceftazidime	> 64		116 (78--172)

*Two doses, 1 and 5 h after infection

** Single dose, 1 h after infection

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†ND=not determined
Source: Table 36, this submission.

Against *S. aureus* Smith, doripenem and imipenem were equally effective, as noted by their similar ED50 values. Treatment of systemic infections caused by methicillin-resistant *S. aureus* (MRSA) revealed that doripenem had the lowest ED50 and MIC values of any of the carbapenems tested; however, vancomycin was the most effective drug tested against MRSA in the mouse systemic infection model and also had the lowest MIC against the MRSA TUH strain used.

Against systemic infections due to penicillin-susceptible and penicillin-resistant *S. pneumoniae*, doripenem had lower ED50 values than meropenem or ceftazidime. Against penicillin-susceptible *S. pneumoniae*, doripenem had a lower ED50 than imipenem but against PRSP, doripenem had a higher ED50 than imipenem.

Mice treated with doripenem and imipenem responded equally in eliminating *S. pyogenes* infections.

The efficacy of doripenem and meropenem were similar in mice infected with *E. faecalis* SR1004. However, imipenem was 9 to 11 times more effective as doripenem and meropenem respectively, which is also reflected in its lower MICs against this organism. All of the carbapenems were more efficacious than ceftazidime in this infection.

Acute Infections Due to Gram-Negative Bacteria

Systemic infections were established by the same methodology detailed in the previous section, **Acute Infections Due to Gram-Negative Bacteria**. For studies using immunocompromised mice with *P. aeruginosa* infections, two i.p. injections of cyclophosphamide were given four days and one day prior to infection.

ED50 values for subcutaneous administered doripenem, meropenem-cilastatin, imipenem-cilastatin, and ceftazidime for treating systemic infections due to Gram-negative bacteria are listed in Table 21.

Table 21. Efficacy of Doripenem against Gram-Negative Organisms in the Mouse Peritonitis Model

Organism (CFU/mouse)	Antibiotic	MIC (µg/ml)	Dosing Frequency	ED50 (95% CI) (mg/kg/dose)
<i>E. coli</i> EC14 (3.2 x 10 ⁵)	Doripenem	0.03	bid*	0.04 (0.003--5.52)
	Meropenem	0.02		0.04 (0.003--5.52)
	Imipenem	0.06		0.21 (0.017--2.49)
	Ceftazidime	0.03		0.08 (0.006--0.93)
<i>E. coli</i> C-11 (9 x 10 ⁵)	Doripenem	0.03	qd**	1.42 (0.65--4.48)
	Meropenem	0.02		0.62 (0.32--20.3)
	Imipenem	0.06		2.41 (1.29--7.04)
	Ceftazidime	2		1.69 (0.86--7.15)

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<i>E. cloacae</i>	Doripenem	0.12	bid*	0.12 (0.09--0.16)
SR12254	Meropenem	0.06		0.09 (0.07--0.12)
CAZ-R	Imipenem	0.5		0.32(0.24--0.42)
^a (1.5 x 10 ⁷)	Ceftazidime	32		7.66 (5.88--9.96)
<i>H. influenzae</i> 88652	Doripenem	0.12	bid*	0.07 (0.04--0.10)
(1.5 x 10 ⁶)	Meropenem	0.06		0.03 (0.02--0.04)
	Imipenem	0.5		0.29 (0.19--0.43)
	Ceftazidime	0.06		0.02 (0.02--0.04)
<i>K. pneumoniae</i>	Doripenem	0.06	bid*	2.49 (1.12--5.56)
SR1	Meropenem	0.03		1.45 (0.65--3.21)
(7.9 x 10 ²)	Imipenem	0.5		2.99 (1.33--6.73)
	Ceftazidime	0.06		0.55 (0.25--1.22)
<i>P. aeruginosa</i>	Doripenem	0.25	bid*	0.17 (0.13--0.24)
SR10411	Meropenem	0.5		0.19 (0.14--0.26)
(1.1 x 10 ⁴)	Imipenem	2		0.46 (0.34--0.63)
	Ceftazidime	2		1.56 (1.13--2.15)
<i>P. aeruginosa</i> E7	Doripenem	0.5	qd**	10.0 (0.71--37.7)
(2.5 x 10 ⁴)	Meropenem	0.5		7.11 (3.32--12.1)
	Imipenem	2		7.13 (1.31--15.5)
<i>P. aeruginosa</i>	Doripenem	0.25	bid ‡	0.61 (0.31--1.23)
SR10411 ††	Meropenem	0.5		1.04 (0.54--2.03)
(3.2 x 10 ⁴)	Imipenem	2		1.04 (0.54--2.03)
	Ceftazidime	2		12.9 (6.61--25.3)
<i>P. aeruginosa</i>	Doripenem	0.25	bid*	0.21 (0.01--7.52)
SR10163, CAZ-R	Meropenem	0.5		0.20 (0.07--0.63)
(1.1 x 10 ⁶)	Imipenem	1		0.40 (0.13--1.25)
	Ceftazidime	32		> 128 (ND)
<i>P. aeruginosa</i>	Doripenem	2	qd**	31.2 (15.9--114.4)
TUH302, CAZ-R	Meropenem	4		> 100 (ND)
(3.0 x 10 ⁴)	Imipenem	8		32.4 (17.9--91.1)
	Ceftazidime	64		> 100 (ND)
<i>P. aeruginosa</i>	Doripenem	2	bid †	4.87 (1.68--14.1)
SR4967, CAZ-R	Meropenem	2		6.10 (2.01--18.5)
(3.8 x 10 ⁴)	Imipenem	1		6.10 (2.01--18.5)
	Ceftazidime	32		> 128 (ND)
<i>P. aeruginosa</i>	Doripenem	8	qd**	6.24 (3.41--11.2)
IMP-2, IPM-R ††	Meropenem	32		38.9 (25.2--58.3)
(5.3 x 10 ⁵)	Imipenem	16		2.42 (1.45--4.32)
	Ceftazidime	32		> 100 (ND)
<i>P. vulgaris</i>	Doripenem	0.5	bid*	0.35 (0.27--0.46)
CN329	Meropenem	0.25		0.16 (0.12--0.21)
(1.3 x 10 ⁶)	Imipenem	4		1.41 (1.05--1.90)
	Ceftazidime	0.12		0.06 (0.05--0.08)
<i>S. marcescens</i>	Doripenem	0.5	bid*	0.35 ((0.26--0.48)
SR25547, CAZ-R	Meropenem	0.12		0.22 (0.17--0.29)
(2.5 x 10 ⁵)	Imipenem	2		2.82 (2.09--3.82)
	Ceftazidime	64		22.6 (16.7--30.5)

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* Two doses, 1 and 5 h after infection

** single dose, 1 h after infection

†CAZ-R, ceftazidime-resistant

†† neutropenic mice

‡two doses, 1 and 3 h after infection

‡‡IPM-R, imipenem-resistant due to production of IMP-2 metallo- β -lactamase

Source: Table 37, this submission.

Twice daily treatment was more efficacious than once daily treatment for all compounds studied in mice infected with various isolates of *E. coli*. Doripenem and meropenem had the same ED50 when given twice daily to mice with systemic *E. coli* EC14 infections and were 2-times and 4-times more efficacious than ceftazidime and imipenem respectively. The ED50 values for once daily doripenem were lower than imipenem and ceftazidime but not meropenem.

In mice with ceftazidime-resistant *E. cloacae* systemic infections, similar activity was observed for doripenem and meropenem. These two antibiotics had lower ED50s than imipenem or ceftazidime.

Carbapenem treatment of systemic infections caused by *H. influenzae* 88652 resulted in similar ED50s for doripenem, meropenem, and ceftazidime (< 0.07 mg/kg). The ED50 for ceftazadime was the lowest of the four antibiotics tested.

Against *K. pneumoniae* SR1, the ED50 values for all of the carbapenems tested were similar (< 3 mg/kg); however, twice daily ceftazidime treatment in this model resulted in an ED50 that was as much as five times lower than the carbapenems.

In healthy, immunocompetent mice with systemic *P. aeruginosa* infections, there appeared to be differences in efficacy related to the dosing regimen. Doripenem, meropenem, imipenem, and ceftazidime were evaluated by two investigators using different strains of *P. aeruginosa* at similar inocula. The first study evaluated the efficacy of doripenem, meropenem, imipenem, and ceftazidime against *P. aeruginosa* SR10411 when the mice were treated 1 and 5 h after infection. In this study, the efficacy, as measured by ED50 values, was improved as much as 60-fold compared to the other studies, where the treatment was given once-daily, 1 h after infection. However, strain differences are probably a major contributing factor.

Against ceftazidime-susceptible strains, the efficacy of doripenem and meropenem was similar when treating an infection with *P. aeruginosa* SR10411. The ED50 values of imipenem and ceftazidime were approximately 3- or 9-fold higher than doripenem or meropenem. In mice infected with *P. aeruginosa* E7, the efficacy of doripenem, meropenem, or imipenem was similar. When *P. aeruginosa* SR10411 was tested in an immunocompromised mouse model, the ED50 values for the carbapenems were 2.3 to 5.5 times higher than those obtained in normal mice infected with the same strain, whereas the ED50 for ceftazidime increased 8-fold.

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Two studies were reported using ceftazidime-resistant strains of *P. aeruginosa* in healthy mice. One study examined the efficacy of doripenem, meropenem, imipenem, and ceftazidime when dosed one h after infection, while the other study examined the effect of two doses, 1 and 5 h after infection. Although both studies used a ceftazidime-resistant strain of *P. aeruginosa*, the carbapenem MICs were 8-fold lower against strain SR10163. In that study, the efficacy of doripenem was similar to meropenem and imipenem when used to treat mice infected with *P. aeruginosa* SR10163. In the study which examined the effect of a single dose on ceftazidime-resistant *P. aeruginosa* TUH302 with elevated carbapenem MICs in the high susceptible range, doripenem and imipenem showed similar efficacy and both were more effective than meropenem or ceftazidime in this model.

Doripenem was more effective than meropenem in IMP-2 metallo- β -lactamase-producing imipenem-resistant *P. aeruginosa*, but was still not as effective as imipenem when given s.c. 1 h after infection. This was unexpected to the Applicant; as the doripenem MIC was 2-fold lower than for imipenem. Ceftazidime showed reduced activity *in vitro* and *in vivo* against this strain.

Against a systemic infection with *P. vulgaris* CN329 a correlation was noted between MIC and ED50 values for doripenem, meropenem, imipenem, and ceftazidime. Doripenem showed slightly better efficacy than imipenem but was not as effective as meropenem in this model, in line with their MICs against this organism. Ceftazidime in the model had both the lowest ED50 and MIC values of all the β -lactams tested.

Animals infected with ceftazidime-resistant *S. marcescens* responded similarly to doripenem or meropenem. Treatment with imipenem or ceftazidime resulted in an 8- or 64-fold increase in ED50, respectively, compared to doripenem.

Overall, doripenem displayed *in vivo* efficacy that was similar to or better than meropenem or imipenem against a variety of Gram-negative strains including imipenem- and ceftazidime-resistant strains.

Murine Neutropenic Thigh Infection Model

Doripenem has been studied in a standard neutropenic thigh model infection. Female Swiss ICR mice were rendered neutropenic by two i.p. injections of cyclophosphamide four days and one day prior to infection. Mice were infected by an i.m. injection of *S. pneumoniae*, *S. aureus*, *E. coli*, *K. pneumoniae*, *E. cloacae* and *P. aeruginosa*, and then given doripenem s.c. at 3, 6, 12, and 24 h dosing intervals. Twenty-four hours after infection, mice were euthanized, muscle excised, and colonies enumerated. The maximum effective dose (Emax), the dose (P50) required to obtain 50% of the Emax, and the slope of the dose response curve were calculated and used to predict the static dose (SD), the dose to achieve a one or two log reduction in bacterial load.

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The efficacy of doripenem on thigh infections in neutropenic mice following subcutaneous treatment is listed in Table 22.

Table 22. Doripenem *In Vitro* and *In Vivo* Activity in the Murine Thigh Infection Model

Organism	MIC ($\mu\text{g/ml}$)	Static Dose (mg/kg)	1 Log_{10} Kill (mg/kg)	2 Log_{10} Kill (mg/kg)
<i>S. pneumoniae</i> 6301	0.004	0.01	0.06	0.59
<i>S. pneumoniae</i> MNO418	0.004	0.21	0.89	5.42
<i>S. pneumoniae</i> 10813	0.004	0.08	0.21	0.49
<i>S. pneumoniae</i> 1396	0.12	1.22	2.45	6.86
<i>S. pneumoniae</i> 1293	0.25	11.0	93	NA ^a
<i>S. pneumoniae</i> 145	0.50	2.40	3.19	4.54
<i>S. pneumoniae</i> 146	0.50	4.97	10.5	25.2
<i>S. aureus</i> 25923	0.015	4.09	12.9	57.9
<i>S. aureus</i> Smith	0.015	1.05	1.82	3.18
<i>S. aureus</i> 307192 (MRSA)	4.0	362	494	882
<i>E. coli</i> 25922	0.015	22.1	113	NA
<i>E. coli</i> 145	0.03	6.15	12.4	253
<i>E. coli</i> 154	0.06	7.32	24.7	97.4
<i>K. pneumoniae</i> 43816	0.06	29	75.3	210
<i>K. pneumoniae</i> 51504	0.06	55.6	216	NA
<i>K. pneumoniae</i> 149	0.06	26.3	56.4	116
<i>K. pneumoniae</i> 152	0.06	12.6	98	1110
<i>E. cloacae</i> 31-59a	0.25	38.3	158	1070
<i>E. cloacae</i> 31-54a	0.50	23.7	78.4	276
<i>P. aeruginosa</i> 27853	0.50	46	100	245

^aNot available

Source: Table 44, this submission.

In Gram-positive bacteria, the dose required to produce a static effect, ranged from 0.1 to 362 mg/kg. The dose of doripenem required to produce a 1 or 2 log₁₀ reduction in bacterial load with Gram-positive organisms ranged from 0.06 to 93 mg/kg (1 log₁₀ reduction) to 0.49 to 57.9 mg/kg (2 log₁₀ reduction). A MRSA strain (*S. aureus* 307192) with a doripenem MIC of 4 $\mu\text{g/ml}$ required at least a nine-fold higher dose to achieve similar killing effects. In Gram-negative bacteria, the dose required for a static effect, 1- log₁₀ reduction, and 2- log₁₀ reduction ranged from 6.2 – 55.6 mg/kg (static effect), 12.4 to 216 mg/kg (1 log₁₀ reduction) to 97.4 to 1111 mg/kg (2 log₁₀ reduction).

The effect of the doripenem dosing interval was studied in this model using *S. aureus* 29213, *S. pneumoniae* 10813, and *K. pneumoniae* 43816. Doripenem was given to infected animals every 3, 6, 12, and 24 h. When doripenem was dosed more frequently, increased efficacy was observed against all organisms tested, concordant with the pharmacodynamic behavior of carbapenems where $T > \text{MIC}$ is the pharmacodynamic index that best predicts efficacy. Reduction in bacterial load was dose-related; the maximum reduction in CFU/g thigh tissue against *S. aureus* 29213, *S. pneumoniae*

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10813, and *K. pneumoniae* 43816 was ~ 3, 6, and 4 log₁₀ CFU/g thigh tissue respectively.

Urinary Tract Infections

Urinary tract infections were established by inoculating ceftazidime-resistant *P. aeruginosa* into the bladder of anesthetized female ICR mice. After infecting each mouse the external urethral orifice was closed for 4 h. Mice were given subcutaneous doripenem, meropenem, imipenem or ceftazidime, with an equimolar concentration of cilastatin added to meropenem and imipenem. Mice were euthanized, kidneys removed, colonies counted and compared to the control group.

The bacterial counts in kidney tissue remaining after four days of treatment with doripenem, meropenem-cilastatin, imipenem-cilastatin or ceftazidime are listed in Table 23.

Table 23. Efficacy of Carbapenems and Ceftazidime Against Urinary Tract Infections Caused by Ceftazidime-Resistant *P. aeruginosa*

Organism (CFU/mouse)	Compound ^a	MIC (µg/ml)	Dose (mg/kg/dose)	Log ₁₀ CFU/g kidney ± SD
<i>P. aeruginosa</i> SRI0163 CAZ-R (3.3 x 10 ⁵)	Control		0	7.94 ± 0.27
	Doripenem	0.25	1	7.20 ± 0.23
			3	4.68 ± 2.55 ^b
			10	3.04 ± 1.87 ^b
			30	1.35 ± 0.05 ^b
	Meropenem	0.5	1	3.74 ± 2.96 ^b
			3	4.60 ± 2.53 ^c
			10	1.95 ± 1.40 ^b
			30	1.86 ± 1.42 ^b
	Imipenem	1	1	5.23 ± 2.76
			3	6.29 ± 2.23
			10	5.31 ± 2.00
			30	4.24 ± 2.45 ^b
	Ceftazidime	32	30	6.39 ± 2.25

a: two doses, 6 and 10 h after infection on the first day, then 2 times per day for 3 days

b: P < 0.01 (vs. control, Dunnett's multiple comparison method)

c: P < 0.05 (vs. control, Dunnett's multiple comparison method)

Source: Table 41, this submission.

Doripenem was significantly different (P < 0.01) from the control at doses of 3, 10, and 30 mg/kg. There were also significant differences from the control in animals treated with meropenem at 1 (P < 0.01), 3 (P < 0.05), 10 (P < 0.01), and 30 (P < 0.01) mg/kg. The only significant difference with imipenem from the control group was seen in mice

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treated with 30 mg/kg ($P < 0.01$). Doripenem and meropenem had similar efficacies between the doses of 3 and 30 mg/kg and both drugs were more efficacious than imipenem or ceftazidime, although the MICs for these drugs were higher than doripenem or meropenem.

Reviewer's comments: To test the *in vivo* efficacy of doripenem, the Applicant explored several animal models of efficacy. In a standard mouse protection peritonitis model, doripenem demonstrated therapeutic effectiveness against both Gram-positive and Gram-negative bacterial infections. For a majority of the isolates tested, the dose demonstrating efficacy in 50% of animals (ED50) of doripenem was low, regardless of whether it was administered as a single dose, or two to three sequential doses; however more drug was usually required for a single dose to achieve efficacy.

In addition, the Applicant explored the efficacy of doripenem in a murine neutropenic thigh infection model. Doripenem displayed dose-related effectiveness with respect to reduction of bacterial burden and increase in survival rate. In a urinary tract model, doripenem was efficacious against pathogens such as CAZ-resistant *P. aeruginosa*. In all animal models evaluated, the efficacy of doripenem was generally equal to or better than those of the control agents such as imipenem, meropenem, and ceftazidime.

The Applicant also performed *in vivo* testing in other models of animal efficacy including: pulmonary infection model, endocarditis, meningitis and intrauterine model. These data were not critical to the indications and thus, not reviewed.

ANIMAL PHARMACOKINETICS

Doripenem was administered intravenously in saline solution and therefore it is considered completely absorbed and bioavailable.

Pharmacokinetic parameters of doripenem were determined in mice, rats, rabbits, dogs, and monkeys receiving a single bolus i.v. or short infusion doses of 20 mg/kg of doripenem (Module 2.6.4, Section 3.1, this submission). Plasma elimination half-life ($t_{1/2}$) was short in rodents with 0.2 and 0.1 hour in mice and rats, respectively. The $t_{1/2}$ was slightly longer in non-rodent species with 0.2 to 1.0, 1.0, and 0.8 hour in rabbits, dogs, and monkeys, respectively, indicating there were inter-species differences in the elimination of doripenem from the plasma. The AUC of doripenem was highest in dogs (78.6 $\mu\text{g}\cdot\text{hr}/\text{mL}$) followed by rabbits (47.9 $\mu\text{g}\cdot\text{hr}/\text{mL}$), monkeys (44.1 $\mu\text{g}\cdot\text{hr}/\text{mL}$), mice (14.1 $\mu\text{g}\cdot\text{hr}/\text{mL}$), and rats (9.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$). The $t_{1/2}$ and AUC of doripenem in female rats following a single i.v. dose at 20 mg/kg were no different from those in male rats.

In repeat-dose studies in rats, rabbits and dogs, doripenem displayed dose-proportional plasma kinetics similar to those after single-dose administration. In conformity with the short half-lives, exposure levels on the last administration day were similar to those after single dosing, indicating that doripenem does not accumulate after repeat dosing. No sex-related differences in plasma kinetics were seen in these studies. The pharmacokinetic

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parameters of doripenem were compared with those of imipenem/cilastatin. There were no marked differences between the two antibiotics (Table 24).

Table 24. Comparison of Pharmacokinetic Parameters of Doripenem with Imipenem/Cilastatin

	Doripenem (20 mg/kg)	Imipenem/Cilastatin (20 mg/kg)
AUC (µg-hr/mL)		
Mice	14.1	19.9 ^a
Rats	9.3	-
Rabbits	47.9	45.7
Dogs	78.6	65.1
Monkeys	44.1	58.0
Humans ^b	79.5	-
t_{1/2} (hr)		
Mice	0.2	0.2
Rats	0.1	-
Rabbits	0.2-1.0	0.5
Dogs	1.0	0.8
Monkeys	0.8	0.7
Humans ^b	1.0	-

^a AUC of imipenem ^b 4-hour infusion time for 500 mg human dose (AUC_{0-24h} 79.5 µg-h/mL; t_{1/2} 1.05 h)
Source: Table 3, Non-clinical overview, this submission.

The AUC of doripenem increased dose-proportionally following a single i.v. dose to mice at 5, 10, 20, 50, or 100 mg/kg, rats at 5, 20, and 40 mg/kg, and monkeys at 5, 10, 20, or 50 mg/kg, and the t_{1/2} of the doripenem did not vary substantially with increased doses. The AUC also increased dose-proportionally up to the highest nontoxic dose levels (300 mg/kg in rats, 100 mg/kg in dogs, and 200 mg/kg in rabbits) in repeat-dose toxicokinetic studies in rats, dogs, pregnant rats, and pregnant rabbits. In the pregnant rats administered ¹⁴C-doripenem the plasma concentrations of doripenem-related radioactivity were dose proportionally higher at the 1000-mg/kg dose compared to the 20-mg/kg dose. The AUC for major metabolite M1 (JNJ-39399191; doripenem dicarboxylic acid) in rats was approximately 2-fold higher than that for doripenem. The M1/doripenem ratio was only approximately 0.04 and 0.25 in dogs and rabbits, respectively. In humans the ratio was approximately 0.1 to 0.2.

Distribution

Doripenem was rapidly distributed to the tissues of male mice receiving an i.v. administration of 20 mg/kg, with the highest tissue concentrations in plasma followed by kidneys, liver, lungs, heart, and spleen. Penetration to the brain was much lower than to other tissues, amounting to a level below the limit of quantification (2 µg/g) immediately after administration.

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Following a single i.v. dose of 20 mg/kg of ^{14}C -doripenem to albino rats the radioactivity was rapidly distributed with the highest concentration found in kidneys followed by plasma, blood, trachea, skin, and lungs. Concentrations in the lungs and lymph were comparable to those in the blood, while the concentrations in the other tissues were lower than that in the blood. Penetration to the brain was also minimal in rats and dogs. Radioactivity distributed to the bone decreased slower than that in the blood and remained detectable 7 days after administration. Radioactivity tissue concentrations following repeated i.v. doses of 20 mg/kg/day of ^{14}C -doripenem for 10 days were slightly higher than that in the single-dose study. The radioactivity distributed to the bones is eliminated more slowly than that in the plasma, however, limited retention of ^{14}C -doripenem-related radioactivity was observed. The retention of limited doripenem-related radioactivity concentration in bone does not have toxicology consequences since there was no bone toxicity observed in long-term toxicity studies.

The distribution of ^{14}C -doripenem in pigmented rats was also investigated. In the eye and pigmented skin, the radioactivity declined in parallel to non-pigmented tissues indicating there was no accumulation in melanin-containing tissues.

The distribution of radioactivity in tissues of pregnant rats following a single i.v. dose of 20 mg/kg of ^{14}C -doripenem on Day 19 of gestation was similar to that of the male rats. Per fetus distribution amounted to no more than 0.03% of the dose administered to the dam. The blood exhibited the highest level among the fetal tissues, and the AUC in blood was only 12% of that in the maternal blood, thus, the fetal transfer of doripenem is limited (Module 2.6.4, Section 4.3). The distribution of ^{14}C -doripenem-derived radioactivity in the tissues of pregnant rats following a single i.v. dose of 1000 mg/kg of ^{14}C -doripenem was also similar to that in the male rats (Module 2.6.4, Section 4.3).

Doripenem is not expected to be accumulated in milk. Following a single i.v. dose of ^{14}C -doripenem, the concentration of radioactivity in milk at 30 minutes post-dosing was 6-fold less than that in plasma. Elimination of radioactivity from milk was slower than from plasma and whole blood, however, at 24 hours post-dosing, doripenem concentration in milk fell to approximately 1/17th of its peak 30-minute value.

The plasma protein binding of doripenem in all nonclinical species ranged from 6.1 to 35.2% and was low at 8.1% in humans. Thus, the potential for drug-drug interaction with co-medications due to plasma protein binding is minimal.

Metabolism

The TLC-bioautograms of the plasma and urine of mice, rats, rabbits, dogs, and monkeys receiving doripenem exhibited only a single antimicrobial spot corresponding to the unchanged parent drug, and no active metabolites were identified. An analysis of the urine of rats treated with ^{14}C -doripenem identified, in addition to the parent drug, the M-1 metabolite of doripenem (JNJ-39399191; doripenem dicarboxylic acid; doripenem-DC). JNJ-39399191 is a β -lactam ring opened metabolite (Figure 1, this submission, not

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shown), which exhibited no antimicrobial activities. JNJ-39399191 was the major metabolite identified in the plasma and urine of dogs, monkeys and humans. Rats produced substantially more JNJ-39399191 than dogs, monkeys, rabbits and human. JNJ-39399191 is identical to doripenem impurity (DP-1), a primary degradation product of doripenem drug substance and drug product.

The *in vivo* mass balance studies with ¹⁴C-doripenem in rats, dogs, and humans confirmed that the majority of the doripenem-related radioactivity was excreted in the urine. Doripenem was predominantly metabolized through hydrolysis to yield JNJ-39399191 across all species.

The hydrolysis of doripenem was indicated to be catalyzed by DHP-I. Lung homogenate of rats exhibited an intrinsic clearance (V_{max}/K_m) approximately 4 times that of the rat kidney homogenate. DHP-I activity in rat tissues with the substrate glycyldehydrophenylalanine was the highest in lungs followed by kidneys and liver, a finding consistent with the rate of metabolism of doripenem. Cilastatin is a DHP-I inhibitor, which exhibited inhibition constants of 0.33 μ M and 1.06 μ M against the hydrolytic activity of doripenem in rat lungs and kidneys, respectively. The concomitant administration of cilastatin and doripenem to rats and monkeys markedly reduced the AUC and urinary excretion rate of JNJ-39399191. It is concluded that the enzyme responsible for doripenem metabolism is DHP-I and the hydrolysis of doripenem by DHP-I in lungs and kidneys contributed to the high clearance of doripenem in rats.

Since the predominant excretion pathway of doripenem is the urine, the metabolism of doripenem by renal DHP-I was investigated using kidney homogenates from mice, rats, dogs, rabbits, and monkeys. Doripenem was relatively metabolically stable in the kidney homogenates from each species, comparable to or better than meropenem or imipenem. Further investigation of the metabolic stability of doripenem using DHP-I purified from mouse kidneys also revealed that doripenem was more metabolically stable than meropenem and imipenem. In addition, human recombinant renal DHP-I (purified from COS1 cells) hydrolyzed 80% of imipenem in 90 minutes, but only 20% of doripenem or meropenem (Table 25). Taken together, the metabolic stability of doripenem to human renal DHP-I is much higher than that of imipenem and comparable to that of meropenem suggesting that doripenem can be administered as a monotherapy to humans similar to meropenem and biapenem.

Table 25. Metabolic Stability of Doripenem to Human Renal DHP-I

DHP-I activity	Proportion Remaining after Incubation for 90 Minutes (%)		
	Doripenem	Meropenem	Imipenem
Human renal DHP-I (0.174 unit/mL)	87.5	79.1	50.4
Human renal DHP-I (0.500 unit/mL)	82.4	78.1	23.2

Source: Table 4, Non-clinical overview, this submission.

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The pharmacokinetics of JNJ-39399191 were investigated following a single i.v. dose of 20 mg/kg of doripenem to rats, dogs, and monkeys (Table 26). In rats the plasma AUC and percent urinary excretion of JNJ-39399191 was higher than those of doripenem. The exposure and the percent urinary excretion of JNJ-39399191 in dogs and monkeys are much lower than those in rats, but similar to those in humans.

Table 26. Pharmacokinetic Parameters of Doripenem and JNJ-39399191 in Several Nonclinical Species and in Humans

Animal	Compound	AUC ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	$t_{1/2}$ (hr)	Cumulative Urinary Excretion to 24 hours Post Treatment (%)
Rats	Doripenem	11.54	0.11	38.60 ^d
(20 mg/kg)	JNJ-39399191 ^a	19.51	-	51.97 ^d
Dogs	Doripenem	91.36	1.0	69.85
(20 mg/kg)	JNJ-39399191 ^a	3.83	-	16.09
Monkeys	Doripenem	63.18	0.8	58.57
(20 mg/kg)	JNJ-39399191 ^a	5.72	-	28.97
Humans ^b	Doripenem	34.4	-	76.1
(10 mg/kg)	JNJ-39399191	2.16	-	15.5
Humans ^c	Doripenem	75.5	-	73.3
(20 mg/kg)	JNJ-39399191	5.18	-	17.2

a 5.72 - 28.97 Humans, b Doripenem 34.4 - 76.1 (10 mg/kg) JNJ-39399191 2.16 - 15.5 Humans, c Doripenem 75.5 - 73.3 (20 mg/kg) JNJ-39399191 5.18 - 17.2 a Expressed as doripenem equivalent b Doripenem and JNJ-39399191 were determined after a 30-minute i.v. infusion of 500 mg of doripenem to humans. The AUC of doripenem is the value from the start of to 12 hours after administration, and the AUC of JNJ-39399191 is the value from the start of to 4 hours after administration (Study R1412, Module 2.7.2). c Doripenem and JNJ-39399191 were determined after a 30-minute i.v. infusion of 1000 mg of doripenem to humans. The AUC of doripenem is the value from the start of to 12 hours after administration, and the AUC of JNJ-39399191 is the value from the start of to 4 hour after administration (Study R1412, Module 2.7.2). d Cumulative excretion to 8 hours post treatment.

- = Not calculated

Source: Table 5, Non-clinical overview, this submission.

Doripenem undergoes minimal cytochrome P450 (CYP)-dependent hepatic metabolism. The effects of doripenem and JNJ-39399191 on the CYP isozymes were investigated *in vitro* using human liver microsomes and hepatocytes. At concentrations of 0.3 to 300 $\mu\text{mol}/\text{L}$ (0.1 to 100 $\mu\text{g}/\text{mL}$) doripenem and JNJ-39399191 did not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5 or 4A11. In addition, there was no induction of CYP isozymes in human hepatocytes at concentrations of 1 or 100 $\mu\text{g}/\text{mL}$. The induction of CYP isozymes was also investigated in liver samples collected in 1- and 3-month repeat dose toxicity studies in rats and dogs. No induction of CYP isozymes were found up to the dose of 1000 mg/kg/day in rats and 500 mg/kg/day in dogs. The possibility that doripenem could cause drug-drug interactions due to interactions with liver CYP isozymes is minimal.

Excretion

Urinary excretion was the predominant elimination pathway of doripenem in mice, rats, rabbits, dogs, monkeys and humans. The mechanism of renal excretion was investigated and the findings suggest that excretion in rats, dogs and monkeys takes place mainly

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through glomerular filtration. The effect of probenecid on plasma concentration and urinary excretion of doripenem was investigated in monkeys and rats. In monkeys administered 20 mg/kg doripenem i.v. in combination with oral probenecid, the plasma AUC rose to approximately twice that in monkeys given doripenem alone. Probenecid was without effects on doripenem pharmacokinetics in rats. By using free-flow and stop-flow renal clearance techniques, with and without probenecid treatment, it was determined that doripenem excretion in rabbits is in part due to tubular secretion. In dogs, the glomerular filtration rate (GFR) of doripenem was slightly greater than its excretion rate, suggesting that doripenem undergoes a small degree of tubular reabsorption.

Reviewer's comments: The Applicant has determined pharmacokinetics in a variety of animals including mice, rats, rabbits, dogs, monkeys and humans. When dosed at 20 mg/kg, the AUC ranged from 9.3 mg·hr/ml in rats to 79.5 mg·hr/ml in humans while the $t_{1/2}$ ranged from 0.1 hr in rats to 1.0 hr in humans. In mice, the highest concentrations of drug were in plasma. Plasma protein binding in all species ranged from 6.1 to 35.2% with a binding of 8.1% in humans. Doripenem was metabolized to a microbially inactive metabolite, M-1. The predominant excretion pathway was by the urinary tract.

ANIMAL PHARMACODYNAMICS***In Vitro* Pharmacodynamic Modeling**

An *in vitro* pharmacodynamic model was used to simulate doripenem and meropenem concentrations that approximated the human exposures of each drug after various administration conditions. Dosing regimens of doripenem were 250 mg, b.i.d., 250 mg, t.i.d., 500 mg, b.i.d., and 500 mg, t.i.d. Meropenem dosing simulations were 500 mg, b.i.d., and 1000 mg, b.i.d. Compounds were given for 30 min at 12-h (b.i.d.) or 8-h (t.i.d.) intervals. Bacterial isolates included *S. aureus*, *E. coli*, and *P. aeruginosa*, and the MICs are found in Table 28. Broth was collected and bacterial counts were quantified during simulation at 15 time points from 0 to 24 h. The magnitude of antibacterial activity is presented in Table 27. Maximum killing was defined as the greatest reduction in CFU observed in the 24 h test period. Viable cell reduction was the change in CFU compared to the control group at 24 h. Area above the curve (AAC) was the change in CFU compared to the control group over 24 h calculated as the surface area found by the trapezoid method.

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Table 27. Antibacterial Activity of Doripenem and Meropenem in an *In Vitro* Pharmacodynamic Model

Organism	Compound	MIC (µg/ml)	Dosing Conditions	AAC (Alog CFU* <i>h</i> /ml)	Maximal Killing (Alog CFU/ml)	Viable Cell Reduction (Alog CFU/ml)
<i>S. aureus</i> SR20406	Doripenem	0.06	250 mg, b.i.d.	120.69	≥5.72	≥5.72
			500 mg, b.i.d.	121.83	≥5.72	≥5.72
			250 mg, t.i.d.	119.37	≥5.72	≥5.72
	Meropenem	0.12	500 mg, b.i.d.	121.09	≥5.72	≥5.72
<i>E. coli</i> SR21262	Doripenem	0.03	250 mg, b.i.d.	132.68	≥5.76	≥5.76
			500 mg, b.i.d.	133.80	≥5.76	≥5.76
			250 mg, t.i.d.	133.64	≥5.76	≥5.76
	Meropenem	≤0.02	500 mg, b.i.d.	134.36	≥5.76	≥5.76
<i>P. aeruginosa</i> SR24854	Doripenem	0.5	250 mg, b.i.d.	101.46	5.75	3.05
			500 mg, b.i.d.	108.14	≥6.05	3.52
			250 mg, t.i.d.	113.33	≥6.05	5.05
	Meropenem	1	500 mg, b.i.d.	99.01	5.20	3.32
<i>P. aeruginosa</i> SR24859	Doripenem	1	250 mg, b.i.d.	95.69	≥5.52	3.27
			500 mg, b.i.d.	109.88	≥5.52	5.04
			250 mg, t.i.d.	112.75	≥5.52	≥5.52
	Meropenem	2	500 mg, b.i.d.	95.37	≥5.52	3.06
<i>P. aeruginosa</i> SR24838	Doripenem	2	250 mg, b.i.d.	48.55	3.67	0.76
			500 mg, b.i.d.	52.36	3.52	1.22
			250 mg, t.i.d.	78.61	5.04	2.54
	Meropenem	4	500 mg, b.i.d.	53.14	3.80	1.01
<i>P. aeruginosa</i> SR24826	Doripenem	2	250 mg, b.i.d.	13.53	2.35	-1.90
			500 mg, b.i.d.	14.46	2.14	-1.83
			250 mg, t.i.d.	29.02	2.37	-0.91
	Meropenem	8	500 mg, b.i.d.	17.23	2.52	-1.80
<i>P. aeruginosa</i> SR24826	Doripenem	2	250 mg, t.i.d.	31.75	2.66	-0.78
			500 mg, b.i.d.	11.65	2.10	-2.60
			500 mg, t.i.d.	35.03	2.32	0.68
	Meropenem	8	1000 mg, b.i.d.	13.38	2.19	-2.26
<i>P. aeruginosa</i> SR24817	Doripenem	4	250 mg, t.i.d.	42.19	2.93	0.67
			500 mg, b.i.d.	37.46	2.97	-0.77
			500 mg, t.i.d.	66.13	4.14	1.01
	Meropenem	4	1000 mg, b.i.d.	46.83	3.23	-0.19
<i>P. aeruginosa</i> SR24848	Doripenem	4	250 mg, t.i.d.	25.80	2.41	-1.36
			500 mg, b.i.d.	47.34	3.23	-0.55
			500 mg, t.i.d.	68.50	4.48	1.45
	Meropenem	8	1000 mg, b.i.d.	21.82	2.47	-2.37

Source: Table 46, Microbiology section, this submission.

All dosing simulations with doripenem and meropenem resulted in the elimination of *S. aureus* SR20406 or *E. coli* SR21262 beyond the limit of detection within 8 h, and no re-growth of bacteria was observed. No increased efficacy was noted by increasing the quantity of compound or the dosing frequency.

Against *P. aeruginosa* SR24854, similar efficacy was observed with doripenem 250 mg, b.i.d. and meropenem 500 mg, b.i.d. Slightly better efficacy was obtained when

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doripenem was increased to 500 mg, b.i.d., however the best treatment regimen was doripenem 250 mg, t.i.d. Slight re-growth occurred between 8 to 12 h and again at 18 h. Treatment with doripenem 250 mg, b.i.d. and meropenem 500 mg, b.i.d. resulted in similar antibacterial activity against *P. aeruginosa* SR24859. When the dose was increased to 500 mg or the dosing schedule was changed to t.i.d., increased antibacterial activity was attained. The doripenem treatment group of 250 mg, t.i.d. was beyond the limit of detection by 10 h and generally remained low for the entire test period. Bacterial re-growth was observed with all other treatment groups starting at 8 h and again at 18 h.

Against *P. aeruginosa* SR24838, all of the treatment regimens resulted in approximately a 3 log₁₀ CFU/ml reduction within 8 h. There was a marked decrease in AAC for all of the treatment combinations as compared to the previous, more susceptible strains tested. Despite the lower AAC and higher MICs (doripenem 2 µg/ml; meropenem 4 µg/ml), doripenem 250 mg, t.i.d. reduced the log₁₀ CFU/ml to 1 at 12 and 20 h. Re-growth was observed with all treatment regimens.

The antibacterial activity of doripenem and meropenem against *P. aeruginosa* SR24826 was reduced by comparison to the previous isolates tested. All of the treatment combinations only resulted in a 2 log₁₀ CFU/ml reduction by 4 h and re-growth was observed with all treatment regimens. Doripenem 250 mg, t.i.d. was the most efficacious treatment, reflected in the AAC, which was double that of the other treatment simulations. When the doripenem dose was increased to 500 mg, t.i.d., a similar reduction in CFU/ml was observed as with 250 mg, t.i.d. Despite the increased dose, re-growth occurred for both simulations at approximately 4h following both the second and third doses. Increasing the dose of meropenem from 500 to 1000 b.i.d. had no effect on antibacterial activity.

A 3 to 4 log₁₀ CFU reduction of *P. aeruginosa* SR24817 was attained with all simulations of doripenem or meropenem. The MIC of doripenem and meropenem against *P. aeruginosa* SR24817 was 4 µg/ml. The most efficacious treatment simulation was doripenem 500 mg, t.i.d. Even the meropenem treatment of 1000 mg b.i.d., which by comparison is 25% more drug than the doripenem 500 mg, t.i.d. treatment regimen, did not achieve the antibacterial activity that was observed with doripenem 500 mg, t.i.d.. Re-growth was observed with all treatment regimens.

Against *P. aeruginosa* SR24848, the doripenem 500 mg, t.i.d. dosing combination achieved the greatest antibacterial activity of any of the simulations tested. This combination achieved ~4 log₁₀ CFU/ml reduction by 12 h. Re-growth was seen with all dosing regimens. The rank order in terms of the treatment ability to prevent re-growth was doripenem 500 mg, t.i.d. > doripenem 500 mg, b.i.d. > doripenem 250 mg, t.i.d. > meropenem 1000 mg, b.i.d.

Reviewer's comments: The *in vitro* activity of doripenem versus meropenem against clinical isolates of *E. coli*, *S. aureus* and *P. aeruginosa* was assessed in an *in*

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vitro pharmacodynamic model that simulated human pharmacokinetics following intravenous dosing.

All dosing simulations with doripenem and meropenem resulted in the elimination of *S. aureus* SR20406 or *E. coli* SR21262 beyond the limit of detection within 8 h, and no re-growth of bacteria was observed. No increased efficacy was noted by increasing the quantity of compound or the dosing frequency.

For *P. aeruginosa* isolates displaying doripenem MICs of 4 µg/ml, an increase in activity was observed by changing the dosing regimen to three times a day from two times a day, thus increasing the T > MIC. In isolates with higher MICs, increasing the amount of compound also improved efficacy.

***In Vivo* Pharmacodynamic Modeling**

The pharmacokinetic parameters and the pharmacodynamic effects of doripenem were characterized in neutropenic female Swiss ICR mice. The pharmacokinetic parameters were determined following s.c. administration of doripenem at three doses. Blood was collected at 8 time points ranging from 0.25 to 4 h, and the doripenem plasma concentration determined by agar bioassay. Pharmacodynamic parameters were determined using multiple dosing regimens, varying the dose and dosing interval. Twenty-four h after infection, the mice were euthanized, thighs homogenized, and plated for enumeration of viable bacteria.

Determination of the pharmacokinetic parameters revealed that the elimination half-life (T_{1/2}) ranged from 0.19 to 0.29 h for the three doses tested, but it was not dose related. The T_{1/2} for doses of 9.38, 37.5 and 150 mg/kg were 0.29, 0.19, and 0.22 h, respectively. The plasma C_{max} values for these doses were 2.72, 31.9 and 96 µg/ml, respectively, and the areas under the concentration-time curve (AUC) were 1.65, 11.7 and 53.3 µg*h/ml, respectively. Doripenem was approximately 5% protein bound in mouse plasma, as determined by ultrafiltration.

The *in vivo* post-antibiotic effect (PAE) was evaluated for doripenem against *S. aureus* 29213 and *S. pneumoniae* 10813 in a neutropenic thigh model. One day after the last dose of cyclophosphamide, one or both thighs of mice were infected with the target organism and then treated subcutaneously 2 h later with doripenem. As described above, the thighs were excised and evaluated for bacterial counts. In *S. aureus* 29213, no PAE was noted with the 2.34 or 9.38 mg/kg doses, although a PAE of 8.2 h was observed with the 37.5 mg/kg dose. A non-dose related persistent effect was observed for doripenem in mice inoculated with *S. pneumoniae* 10813, with PAEs for the 2.3, 9.4, and 37.5 mg/kg doses of 0.72, 2.7, and 0 h, respectively.

Multiple dosing regimens of doripenem were evaluated in the neutropenic thigh model to determine the pharmacodynamic effect against selected strains of *S. pneumoniae*, *S. aureus*, *E. coli*, *K. pneumoniae*, *E. cloacae*, and a single strain of *P. aeruginosa*. The slope of the bacterial killing of these studies was used to calculate the bacteriostatic dose.

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The *in vitro*, *in vivo*, and pharmacodynamic results of doripenem against the tested organisms are found in Table 28.

Table 28. Doripenem *In Vitro* and *In Vivo* Activity in the Murine Thigh Infection Model

Organism	MIC (µg/ml)	%T>MIC (Static Effect)	%T>MIC (1 Log ₁₀ Kill)	%T>MIC (2 Log ₁₀ Kill)
<i>S. pneumoniae</i> 6301	0.004	2.3	15	31
<i>S. pneumoniae</i> MNO418	0.004	15	34	47
<i>S. pneumoniae</i> 10813	0.004	17	24	30
<i>S. pneumoniae</i> 1396	0.12	12	17	24
<i>S. pneumoniae</i> 1293	0.25	21	31	ND ^a
<i>S. pneumoniae</i> 145	0.50	7.3	10	12
<i>S. pneumoniae</i> 146	0.50	12.2	16.7	20
Mean ± SD ^b		12.4 ± 6.2	21.1 ± 8.9	27.3 ± 11.9
<i>S. aureus</i> 25923	0.015	35	40	41
<i>S. aureus</i> Smith	0.015	25	29	34
<i>S. aureus</i> 307192	4.0	27	28	31
Mean ± SD		29 ± 5.3	32.3 ± 6.7	35.4 ± 5.0
<i>E. coli</i> 25922	0.015	38	47	ND
<i>E. coli</i> 145	0.03	33	35	51
<i>E. coli</i> 154	0.06	28	30	38
<i>K. pneumoniae</i> 43816	0.06	29	35	46
<i>K. pneumoniae</i> 51504	0.06	34	49	ND
<i>K. pneumoniae</i> 149	0.06	28	34	40
<i>K. pneumoniae</i> 152	0.06	31	39	54
<i>E. cloacae</i> 31-59a	0.25	26	37	47
<i>E. cloacae</i> 31-54a	0.50	20	27	36
<i>P. aeruginosa</i> 27853	0.50	23	28	35
Mean ± SD		29 ± 5.3	36.1 ± 7.4	43.3 ± 7.1

^a Not determined

^b Standard deviation

Source: Table 47, Microbiology section, this submission.

Against *S. pneumoniae* (n=7), the percent of the dosing interval required for doripenem plasma concentrations to be above the MIC (%T>MIC) to produce a static dose, a 1 log₁₀ kill, or a 2 log₁₀ kill of inoculated bacteria was 12, 21 and 27%, respectively. In three isolates of *S. aureus*, the doripenem %T > MIC required for microbiologic effect was slightly higher than that needed for eradication of *S. pneumoniae*, with 29, 32, and 35% of the dosing interval required to produce a static effect, 1 log₁₀ or 2 log₁₀ decrease, respectively, in the *S. aureus* inoculum.

Doripenem was tested against ten isolates of Gram-negative bacteria including *E. coli*, *K. pneumoniae*, *E. cloacae* and *P. aeruginosa*. The doripenem %T > MIC to produce a static effect was essentially the same for the Gram-negative bacteria and *S. aureus*. The percent of the dosing interval in which plasma concentrations of doripenem were required to be above the MIC to produce 1 log₁₀ and 2 log₁₀ decreases in the inoculum were slightly

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longer for Gram-negative bacteria than for *S. aureus*. Mean values for all tested Gram-negative isolates were 29, 36 and 43 % T > MIC to achieve stasis, a 1 log₁₀ and 2 log₁₀ decrease, respectively. The time above MIC required to achieve stasis, a 1 log₁₀ decrease, and a 2 log₁₀ decrease for *P. aeruginosa* was 23%, 28%, and 35% respectively.

In summary, the mean doripenem %T > MICs for bacteriostasis ranged from 12% to 29% for all of the isolates tested. To achieve a 1 or 2 log₁₀ reduction of bacterial counts, the mean doripenem %T > MIC values of 21 to 36% and 27 to 43% were needed, respectively.

Reviewer's Comments: The *in vivo* pharmacodynamic activities of doripenem were characterized in a mouse neutropenic thigh infection model against several Gram-positive and Gram-negative bacterial pathogens. These PK/PD studies revealed that the time above the MIC (T > MIC) was the pharmacokinetic parameter that clearly correlated with *in vivo* efficacy. The magnitude of the PK/PD parameter required to achieve a static effect was relatively similar for the tested bacterial isolates, which included *S. pneumoniae*, *S. aureus*, *E. coli*, *K. pneumoniae*, *E. cloacae* and *P. aeruginosa*. The time above MIC required to achieve a static effect and a 1 log₁₀ reduction for *P. aeruginosa* was 23% and 28%, respectively.

HUMAN PHARMACOKINETICS

The single- and multiple-dose PK of i.v. doripenem have been investigated in several studies in Western and Japanese populations. (For details refer to Module 2.7.2, SCP). Doripenem exhibits predictable, linear, and time-independent pharmacokinetics. In general, PK data in the Japanese and Western populations were similar.

In Western subjects, doripenem PK demonstrated dose proportionality for the investigated 500 and 1,000 mg doses administered either over 1 hour, or as prolonged infusions over 4 hours. In Japanese subjects, doripenem PK was linear over a dose range of 125 to 1,000 mg.

Following the recommended dose of 500 mg doripenem as a 1-hour i.v. infusion, the mean maximum concentration (C_{max}) and area under the concentration curve (AUC) of doripenem across studies was 23.6 µg/mL and 36.9 µg.h/mL, respectively.

Consistent with the short terminal elimination half-life (t_{1/2}) of doripenem (mean across all studies: 69 min), steady state was attained by the second dose for both the 500 and 1,000 mg 1-hour infusions when administered q8h. Doripenem did not accumulate after multiple-dose administration.

Distribution, Metabolism, and Elimination

Doripenem binding to human plasma protein is minimal (8.1%). Thus, a large proportion of the drug remains unbound in plasma and is therefore potentially available for tissue and fluid penetration. The median doripenem apparent steady-state volume of distribution (V_{ss}) in healthy Western subjects was 16.6 L, approximating the extracellular fluid

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volume in humans (18.2 L), which is typical of carbapenems. Doripenem penetrated well into various body tissues and fluids, as assessed in 10 Phase 2 and 3 Japanese studies (Module 2.7.2, SCP, Section 3.1). Even though only 250 mg doses were administered in most of these studies, the doripenem concentrations exceeded 1 to 2 µg/mL (or µg/mg) in most tissues and thus exceeded the MIC for most susceptible bacteria.

A microbiologically inactive dicarboxylic acid metabolite, referred to as doripenem-M-1, was identified in preclinical studies and measured in Phase 1 studies. This metabolite is formed by cleavage of the β-lactam ring, presumably by dehydropeptidase-1. In Western subjects with normal renal function, the mean plasma M-1-to-parent doripenem AUC ratio across studies was 0.183. (Module 2.7.2, SCP, Section 3.2.2, this submission).

Doripenem is rapidly eliminated from plasma in healthy subjects, with a mean $t_{1/2}$ of 69 min that is independent of the dose (500 or 1,000 mg doripenem) and the duration (1 or 4 hours) of the i.v. infusion. The mean doripenem clearance across studies was 15.9 L/hr (265 mL/min) and was reduced in elderly subjects and subjects with renal impairment. Mean urinary recovery of doripenem and doripenem-M-1, expressed as a percentage of the administered doripenem dose, was 69.9% and 15.1%, respectively, and was independent of the administered dose.

Doripenem has multiple elimination routes: it is predominantly eliminated by renal excretion (renal clearance 10.2 L/hr; 170 mL/min), both by glomerular filtration and active tubular secretion, and secondarily via metabolism to the inactive dicarboxylic acid metabolite, doripenem-M-1 by dehydropeptidase-1. Doripenem is not metabolized in the liver and has very little propensity to undergo cytochrome P450-mediated drug interactions.

HUMAN PHARMACODYNAMICS

For doripenem and other carbapenems, the time that the free serum drug concentration exceeds the MIC ($T > MIC$) for the target organism has been established as the PK/PD parameter that correlates best with the therapeutic efficacy.

***In Vivo* PK/PD Relationship**

In vivo efficacy of doripenem is most closely related to the proportion of the dosing interval above the minimum inhibitory concentration ($T > MIC$) of the target pathogen. Doripenem has shown efficacy in various animal models of infection caused by both Gram-positive and Gram-negative bacteria, including anaerobes, and various beta-lactamase-producing strains. In general, the *in vivo* efficacy of doripenem was comparable to that of meropenem and imipenem/cilastatin, as well as other new carbapenems. The animal models used for evaluation included peritonitis, meningitis, endocarditis, UTI, pneumonia, and intrauterine infections.

Doripenem was efficacious against multiple isolates of *S. pneumoniae*, *S. aureus*, *P. aeruginosa* and *Enterobacteriaceae* in a neutropenic mouse thigh infection model. The

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magnitude of $T > MIC$ values required to achieve a bacteriostatic effect (generally $< 30\%$ of the dosing interval) was similar for the tested bacterial isolates, which included *S. aureus*, *E. coli*, *K. pneumoniae*, *E. cloacae* and *P. aeruginosa*, although values were somewhat lower for *S. pneumoniae*.

***In Vitro* PK/PD Modeling**

Based on *in vivo* PK/PD relationships, *in vitro* modeling of human PK can be used to evaluate the antibacterial activity of clinical dosing regimens.

The activity of doripenem against clinical isolates of *E. coli*, *S. aureus* and *P. aeruginosa* was characterized in comparison with meropenem, in an *in vitro* PD model that simulated human pharmacokinetics with i.v. dosing. Although lower doses were effective against highly susceptible bacteria, for *P. aeruginosa* isolates with doripenem MICs of 4 µg/mL, doripenem administered as 500 mg three times a day was required for maximal efficacy. The antibacterial effect of this dosage was greater than that of meropenem 1,000 mg twice a day.

Pharmacokinetic/Pharmacodynamic Target Attainment***Dose Selection for Phase 3 Studies***

In the neutropenic mouse thigh infection model, bacteriostatic effects of doripenem were observed on average when free drug concentrations exceeded the MIC for $\approx 30\%$ of the dosing interval (DORI-M-002). Although the magnitude of the $\%T > MIC$ required for clinical efficacy has not been established for carbapenems, a conservative $\%T > MIC$ of 35% to 40%, associated with maximal bacterial killing in neutropenic animals, was initially used in dose selection for the cIAI and cUTI Phase 3 studies.

Additionally population pharmacokinetic/pharmacodynamic analyses have been done using isolates from the clinical trials. The goal of these analyses was to assess the performance of clinically relevant doripenem dosing regimens in attaining pharmacokinetic/ pharmacodynamic (PK/PD) target exposure metrics. These computations were performed over a range of MIC values and for two clinical dosing regimens using a Monte Carlo simulation method. The population PK model estimated the probability of attaining selected PK/PD targets for various dosing regimens, based on the targets defined from the neutropenic mouse model. In this murine model with a compromised immune system, *in vivo* bacteriostatic effects of doripenem are observed when free drug concentrations exceed the MIC for 30% of the dosing interval. For the calculations performed by the Applicant, two different dosing regimens were evaluated with regard to their probability of attaining $\% T > MIC$ for 25 to 35% of the dosing interval.

The clinically relevant dosing regimens included 500 mg infusions for 1 and 4 h administered every 8 h. Although the 4 h infusion regimen was not used in the cUTI and cIAI indications, this regimen is being studied in one of the nosocomial pneumonia phase 3 trials (DORI-10) and is thus included here for completeness. Computations were

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performed using all the pathogens with susceptibility results isolated during the phase III clinical trials of complicated urinary tract (cUTI) (DORI-05, 06) and intra-abdominal infections (cIAI) (DORI-07 and 08). These collections of organisms represented the natural variability of frequency and susceptibility to doripenem seen in the aforementioned infections.

The species-specific target attainment values were calculated to determine the probability of attaining a specific target at a selected dose of doripenem against a specific pathogen in a defined disease. The target attainment for each pathogen species was weighted by the pathogen's natural frequency of occurrence in each clinical syndrome. Overall summary tables for the doses of 500 mg q8h for a 1-hour and 4-hour infusion for cIAI and cUTI pathogens are presented in Tables 29 and 30.

Table 29. Specific Target Attainment for cIAI Pathogens Based on Doripenem Dosing Regimens.

Species specific target attainment	500 mg, q8h, 1-hour infusion			500 mg, q8h, 4-hour infusion		
	25% T>MIC	30% T>MIC	35% T>MIC	25% T>MIC	30% T>MIC	35% T>MIC
Enterobacteriaceae	100	100	99.98	100	100	100
Non-Enterobacteriaceae	98.1	97.6	96.7	98.2	98.1	98.1
<i>Acinetobacter</i> spp.	85.6	84.2	81.5	85.8	85.8	85.8
<i>Stenotrophomonas maltophilia</i>	1.3	0.7	0.3	0.7	0.5	0.3
<i>Haemophilus</i> spp.	100	100	100	100	100	100
<i>Enterococcus</i> spp.	60.5	49.2	39.4	69.6	68.3	66.6
<i>Staphylococcus</i> spp.	90.5	90.1	89.6	90.8	90.6	90.5
<i>Streptococcus pneumoniae</i>	100	100	100	100	100	100
<i>Streptococcus</i> spp. (not- <i>S. pneumoniae</i>)	100	99.99	99.97	100	100	100
<i>Enterococcus faecalis</i>	78.0	62.6	48.9	90.2	89.1	87.3
Other gram-Positive	80.3	80.1	79.9	80.1	80.1	80.1
All Anaerobes	97.8	97.3	96.9	98.1	98.0	97.9

Source: Table 50, this submission.

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Table 30. Specific Target Attainment for cUTI Pathogens Based on Doripenem Dosing Regimens.

Species specific target attainment	500 mg, q8h, 1-hour infusion			500 mg, q8h, 4-hour infusion		
	25% T>MIC	30% T>MIC	35% T>MIC	25% T>MIC	30% T>MIC	35% T>MIC
Enterobacteriaceae	99.8	99.7	99.6	99.8	99.8	99.8
Non-Enterobacteriaceae	83.6	80.7	77.7	85.8	85.2	84.5
<i>Acinetobacter</i> spp.	99.8	98.5	95.4	100	100	100
<i>Burkholderia cepacia</i>	98.1	90.9	78.3	100	100	100
<i>Enterococcus</i> spp.	74.9	61.1	48.9	85.9	85.6	84.5
<i>Staphylococcus</i> spp.	81.8	78.5	75.1	84.1	84.0	83.8
<i>Streptococcus</i> spp. (not- <i>S. pneumoniae</i>)	100	100	100	100	100	100
<i>Enterococcus faecalis</i>	82.2	67.5	54.5	93.9	93.5	92.2
All Anaerobes	100	100	100	100	100	100

Source: Table 51, this submission.

These data demonstrate that target attainment of 25-35% for the pathogens found in the clinical trials for cIAI and cUTI, e.g., *Enterobacteriaceae*, non-*Enterobacteriaceae*, *Staphylococcus* spp., *S. pneumoniae*, and *Streptococcus* spp. other than *S. pneumoniae*, was in the range one would consider of relevance for *in vivo* efficacy (generally >80%). Target attainment for *Enterococcus* spp. was below 80%; a subanalysis for *E. faecalis* indicated a greater target attainment rate, 82.2, 67.5 and 54.5% for T > MICs of 25, 30 and 35%, respectively, but most T > MIC values were below the relevant rate of 80%.

Median values and the 95 percentile band width of simulated unbound doripenem plasma concentrations following multiple-dose administration of 500 mg doripenem as 1 h intravenous infusion every 8 h are shown in Figure 5. The doripenem medium unbound C_{max} was 20.3 µg/ml with an estimated half-life of 1.48 h. Free drug concentrations were above 4 µg/ml for about 2.5 h when the median plot was considered, and were above this value for over 6 h when the upper 95 percentile curve was taken into consideration. The lower 95 percentile curve was above 4 µg/ml for approximately 1.5 h, i.e., 20% of the dosing interval.

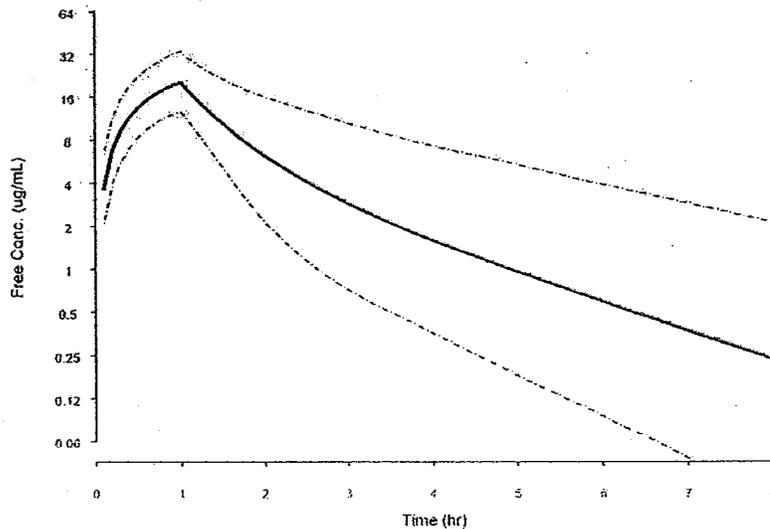
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Figure 5. Median pharmacokinetic curve for 500 mg dose of doripenem given as a 1 h infusion every 8 h

50th % Quantile & 95 Percentile Band for HIV in PK
500 mg, q8h, 1 hr infusion.



Source: Figure 5, this submission.

Additionally, $T > MIC$ target attainment was modeled for a range of targets. These data can be found in Table 31. They demonstrate that there is $> 90\%$ target attainment at $T > MIC$ 30% at a doripenem MIC $< 2 \mu\text{g/ml}$. For doripenem MICs $< 4 \mu\text{g/ml}$, there is 77% target attainment at $T > MIC$ 25%. The largest changes in percent target attainment across the potential targets occurred between 2 and 4 $\mu\text{g/ml}$. The Applicant feels that these data support a breakpoint for doripenem in the 2 to 4 $\mu\text{g/ml}$ range.

Table 31. Target Attainment in cIAI or in cUTI for 500 mg Doripenem Dose, Every 8 h with a 1 h Infusion.

MIC ($\mu\text{g/ml}$)	$T > MIC$ 25%	$T > MIC$ 30%	$T > MIC$ 35%
0.06	100	100	100
0.12	100	100	100
0.25	100	100	100
0.5	100	99.9	99.6
1	99.9	99.0	96.0
2	98.1	90.9	78.3
4	77.3	53.4	34.6
8	19.5	10.0	6.0
16	1.3	0.7	0.3

Source: Table 52, this submission.

Reviewer's comments: The Applicant presents the results of several studies of human pharmacokinetics and pharmacodynamics. Doripenem binds to human plasma protein at a low rate of 8.1%. With a large proportion of the drug free in plasma, much of the drug is potentially available for tissue and fluid penetration.

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The median doripenem steady-state volume of distribution in healthy adults was 16.6 L, approximately the extracellular fluid volume in humans (18.2 L). Doripenem concentrations ranged from 1 to 2 µg/ml in most tissues, thus exceeding the MIC for most susceptible bacteria. The drug is metabolized to produce a microbiologically inactive compound, doripenem M-1. Doripenem is rapidly eliminated with a mean $t_{1/2}$ = 69 min that is independent of the dose or duration of intravenous infusion. The main route of elimination is via the urinary tract.

The $T > MIC$ is the pharmacokinetic/pharmacodynamic parameter for doripenem that best correlates with therapeutic efficacy. The $T > MIC$ values required to achieve a bacteriostatic effect are approximately 30% of the dosing interval.

Monte Carlo simulations were used to determine species specific PK/PD target attainments for pathogens responsible for cUTI or cIAI. These data demonstrate that target attainments of 25-35% for these pathogens e.g., *Enterobacteriaceae*, non-*Enterobacteriaceae*, *Staphylococcus* spp., *S. pneumoniae*, and *Streptococcus* spp. other than *S. pneumoniae*, were in the range considered of relevance for *in vivo* efficacy (generally >80%). However, target attainment for *Enterococcus* spp. was below 80%; a subanalysis for *E. faecalis* indicated a greater target attainment rate, 82.2, 67.5 and 54.5% for $T > MIC$ s of 25, 30 and 35%, respectively, but most $T > MIC$ values were below the relevant rate of 80%.

CLINICAL SUSCEPTIBILITY TEST METHODS**Disk and Broth Dilution Susceptibility Test Methods**

Susceptibility test methods for doripenem have been established. Initial work evaluated preliminary quality control and disk mass. Quality control ranges for disk and MIC testing were published and ranges were approved by CLSI in June of 2004. These are currently available in the CLSI documents, including the anaerobe quality control ranges that appear in the 2007 version of the M11 anaerobe document.

In establishing disk mass, correlation with MIC values is required. These correlations provided the basis for the initial provisional interpretive criteria for doripenem, which were based on the microbiologic characteristics of the bacterial populations tested, but did not take into account pharmacokinetics, pharmacodynamic or the MIC correlation with clinical or bacteriologic outcome. Lacking these two critical components, Jones et al. and Wexler proposed common breakpoints of Susceptible = 4 µg/ml and Resistant = 16 µg/ml for doripenem for aerobic and anaerobic bacteria. Brown and Tracjewski conducted a large study (over 2000 isolates) correlating MIC and disk values, and proposed breakpoints for most organisms: Susceptible, =2 µg/ml; generally a broad intermediate range of 4-8 µg/ml; and the same resistant range of =16 µg/ml as defined by Jones and Wexler. These tentative breakpoints provided a framework for analysis for further studies.

Pharmacodynamic analyses including animal model analysis in the neutropenic thigh model and sophisticated modeling to assist dose selection for phase II and III were also done. These studies demonstrated that $T > MIC$ is the best predictor of clinical outcome

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(key pharmacodynamic index) for doripenem and suggested that the pharmacodynamics of doripenem were consistent with a susceptible breakpoint in the range of 2-4 µg/ml. The final critical component in establishing final breakpoints, involving correlation of MIC with clinical and microbiologic outcome from the doripenem pivotal clinical trials, will be presented later in the appropriate section of this Microbiology Summary (Correlation of Provisional Criteria with Clinical Outcome).

QUALITY CONTROL PARAMETERS

Studies by Brown, et al and Jones et al were performed to evaluate the susceptibility of a broad range of organisms, in an attempt to recommend preliminary quality control ranges and interpretive criteria for doripenem. These studies were conducted according to the standard methodology established and published by the Clinical and Laboratory Standards Institute (CLSI, formerly known as NCCLS, or National Committee on Clinical Laboratory Standards) in CLSI or NCCLS Documents M2, M7, M11, and M23. The studies provided tentative interpretive criteria and established quality control ranges. The 10 µg doripenem disk, the "class" disk concentration used for ertapenem, imipenem, and meropenem, was shown to be suitable for use.

The Brown study was an eight laboratory distributive study that included hospital and commercial laboratories. It followed the standard design for CLSI quality control study protocols for MIC, disk, and agar dilution for anaerobic organisms. Ten quality control organisms recommended by CLSI were tested. These were:

- *E. coli* ATCC 25922,
- *S. aureus* ATCC 29213,
- *S. aureus* ATCC 25923,
- *E. faecalis* ATCC 29212,
- *P. aeruginosa* ATCC 27853,
- *S. pneumoniae* ATCC 49619,
- *H. influenzae* ATCC 49247,
- *H. influenzae* ATCC 49766,
- *B. fragilis* ATCC 25285,
- *B. thetaiotaomicron* ATCC 29741, and
- *Eubacterium lentum* ATCC 43055.

The proposed MIC and zone diameter ranges are presented in Tables 32 and 33 (this submission). Quality control ranges were presented to the CLSI Subcommittee on Antimicrobial Susceptibility Testing (June 13-15, 2004, Boston, MA).

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Table 32. Microdilution Broth Quality Control Results from an Eight Lab Study

Table 1. Doripenem MIC quality control

Quality control strain	Number of occurrences at the following MIC (mg/L) ^{a,b}															
	0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
<i>E. coli</i> ATCC 25922	0	0	1	54	177	8	0	0	0	0	0	0	0	0	0	0
<i>S. aureus</i> ATCC 29213	0	0	3	70	163	2	0	0	0	0	0	0	0	0	0	0
<i>E. faecalis</i> ATCC 29212	0	0	0	0	0	0	0	0	0	3	231	6	0	0	0	0
<i>P. aeruginosa</i> ATCC 27853	0	0	0	0	0	0	5	164	40	1	0	0	0	0	0	0
<i>S. pneumoniae</i> ATCC 49619	0	0	1	7	63	169	0	0	0	0	0	0	0	0	0	0
<i>H. influenzae</i> ATCC 49766	0	0	0	0	2	26	211	1	0	0	0	0	0	0	0	0
<i>B. fragilis</i> ATCC 25285	7	0	0	0	2	3	57	174	0	0	0	0	0	0	0	0
<i>B. thetaiotaomicron</i> ATCC 29741	0	1	1	1	1	2	4	120	86	1	0	0	0	0	0	0
<i>E. lentum</i> ATCC 43055	no range recommended															

^aNumber value represents the limit of MIC dilutions tested

^bRecommended quality control ranges represented in bold.

Source: Table 32, this submission.

Table 33. Disk Diffusion Quality Control Results from an Eight Lab Study

Table 2. Doripenem disk diffusion quality control

Quality control strain	No. of occurrences at the following zone diameters (mm) ^a																			
	<20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
<i>E. coli</i> ATCC 25922								1	9	24	25	86	112	97	67	42	14	3		
<i>S. aureus</i> ATCC 25923													9	18	43	60	61	62	67	53
<i>P. aeruginosa</i> ATCC 27853					1				1	18	60	127	87	69	19	1	1			
<i>S. pneumoniae</i> ATCC 49619								1	5	21	52	87	90	74	71	35	18	9	4	7
<i>H. influenzae</i> ATCC 49247	7	10	29	22	43	87	107	75	42	12	20	10	9	2	1	1				

^aRecommended quality control ranges represented in bold.

Source: Table 33, this submission.

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CLSI approved the quality control ranges for doripenem for all organisms with the exception of *E. lentum* ATCC 43055 where the QC ranges would have been too broad. This organism has consistently performed poorly as a quality control organism for other antibiotics, and CLSI is in the process of identifying an alternative Gram-positive anaerobic quality control organism.

The quality control ranges determined from the data by this Reviewer are presented in Table 34 below.

Table 34. Doripenem Quality Control Ranges

QC Isolate	ATCC #	Disk Diffusion	Minimum Inhibitory
		Zone diameter (mm)	Concentration (µg/ml)
<i>E. coli</i>	25922	—	0.0 — 0.06
/	/	+	/
<i>P. aeruginosa</i>	27853	/	0.12-0.5
<i>S. pneumoniae</i>	49619	/	—
/	/	—	—
<i>B. fragilis</i>	25285	—	—
<i>B. thetaiotaomicron</i>	29741	—	0.12- —

Source: Table 32 and 33 and Appendices 3.1 and 3.2, this submission.

Development of Interpretive Criteria and QC Parameters for MIC Testing

Jones et al and Wexler et al proposed interpretative criteria for doripenem using MICs of < 4 µg/ml as susceptible and >16 µg/ml as resistant (Table 35), comparable to those for imipenem and meropenem. However, Brown suggested a susceptible breakpoint of < 2 µg/ml for most organisms, with 1 µg/ml for streptococci. Bhavnani et al. proposed a conservative target for doripenem, using $T > 35\%$ of the dosing interval for 500 mg administered over 1 h every 8 h, indicating that efficacy was probable for organisms with doripenem MICs < 2 µg/ml. This target is higher than the proposed bacteriostatic targets of > 20% $T > MIC$ for carbapenems based on PK/PD modeling. The establishment of final breakpoints will take into consideration multiple factors, including microbial MIC distributions, pharmacokinetics, pharmacodynamic properties, and importantly, the results of the microbiology outcomes from the Phase 3 clinical trials.

Development of Interpretive Criteria and QC Parameters for Disk Testing

Two different sets of breakpoints have appeared in the published literature for doripenem. Wexler and the Jones group have proposed interpretive criteria based on the breakpoints published for imipenem and meropenem, with susceptible defined as doripenem MICs < 4 µg/ml and resistance defined with MICs >16 µg/ml. Brown and Traczewski proposed tentative disk diffusion interpretative criteria based on scattergrams comparing doripenem MICs versus zone diameters (10 µg disks). The MIC susceptible breakpoints

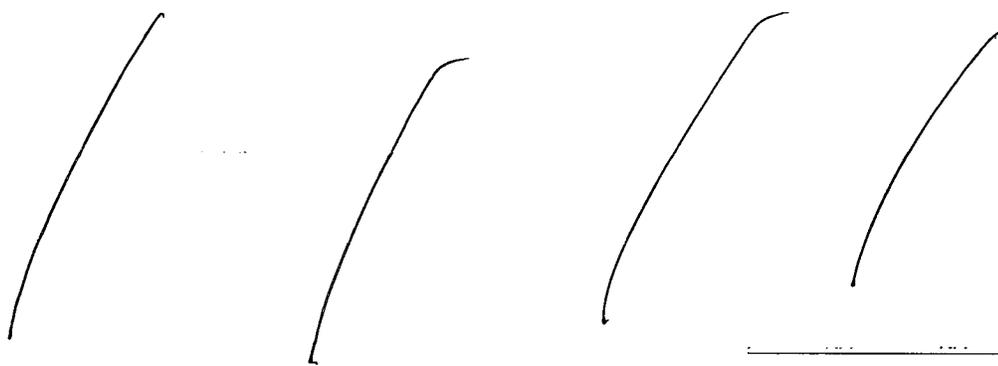
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chosen by Brown were generally $< 2 \mu\text{g/ml}$ for most organisms, and $1 \mu\text{g/ml}$ for streptococci. The proposed preliminary disk diffusion breakpoints for doripenem are shown in Table 35. Final disk breakpoints will be established by comparing MIC and disk data from isolates from the clinical trial and by comparing/including the MIC versus disk data from the Brown study in order to add increased numbers of organisms.

Table 35: Tentative Doripenem MIC Breakpoints and Zone Diameter Breakpoints, Based on Population Distributions or Parity with Other Carbapenems (Applicant Determined)

**Penicillin Binding Assays**

Penicillin-binding studies for doripenem were conducted using a competition assay with the fluorescent penicillin Bicillin FL47, rather than using radiolabeled benzylpenicillin as described for the other carbapenems. In this method whole cells or cell membranes are incubated with the carbapenem to allow for acylation of the PBP before incubation with Bicillin FL in a competition assay.

***In Vitro* Susceptibility Testing Methods**

Approximately 10,000 isolates from the US, Japan and Europe were tested for their susceptibility to doripenem. An additional 50,000 isolates were gathered through world surveillance programs (2003—2005) in North America, Latin America and Europe. Standardized susceptibility tests following the guidelines of the CLSI were performed with doripenem at major microbiology laboratories in the US and the UK (Table 36).

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Table 36. Laboratories and Methods Used for Doripenem Susceptibility Testing

Test Lab or Organization	Isolate Collection Date	# of Isolates	Test Methods	Date Study Completed	Applicant Reference
US					
	2001-02	1296	Agar, Broth	Sep-02	2, 22
	1999-03	815	Broth	Jul-03	1
	1998-03	205	Broth*	Jul-03	28
	1999-02**	2137	Broth	Jan-04	21, 26
	1974-03	364	Agar	Nov-03	5
	1994-03	194	Broth*	Nov-03	29
	2001-03	600	Broth	2004	33
	1983-2004	110	Agar	2006	27A
Japan					
	1996	1117	Agar	2002	24
	1997-98	135	Agar	2000	27
	1997	202	Broth	2000	23
	not specified	978	Broth	1997	25
UK					
	1994-02	250***	Agar	Jul-03	30, 34, 35
	<i>Surveillance (North America, Latin America, Europe)</i>				
	2003	16,008	Broth	Jul-04	1
	2004	17,774	Broth	Dec-05	36
	2005	17,682	Broth	Jul-06	17
	2005-06	19,264	Broth	2006	37A
2005	2706	Agar	Dec-05	37B	

Source: Table 1, Clinical Microbiology Studies, 04 June 2007 submission.

MBC and Time-Kill Studies

For the MBC (minimum bactericidal activity) studies, CLSI methodology was used to evaluate bactericidal activity against (a) 20 isolates each of *S. aureus*, *E. coli* and *P. aeruginosa* with doripenem and comparator antibiotics; and (b) against 10 individual Gram-positive and Gram-negative clinical isolates.

Time-kill experiments were conducted with doripenem, meropenem, imipenem and ceftazidime against a single *S. aureus*, *E. coli* and *P. aeruginosa* isolate, with doripenem against five *P. aeruginosa* isolates, and with doripenem against *S. aureus* (N = 2), *E. faecalis* (N = 1), *S. pneumoniae* (N = 1), *E. coli* (N = 2), *K. pneumoniae* (N = 1), *E. cloacae* (N = 1), *P. aeruginosa* (N = 1) and *A. baumannii* (N = 1) isolates. All time-kill experiments were conducted in broth under appropriate culture conditions for respective isolates, at antibiotic concentrations 2-, 4- and 8-times the MIC. In time-kill studies, doripenem demonstrated bactericidal (> 3 log₁₀ decrease in CFU/ml) activity within 6 or 8 h at 4- or 8-times the MIC against most tested isolates, including *S. aureus*, *E. coli*, *P. aeruginosa*, *S. pneumoniae* and *E. cloacae*.

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***In Vivo* Postantibiotic Effect in a Mouse Respiratory Infection Model**

Mice were given intraperitoneal (i.p.) cyclophosphamide four days and one day prior to infection, then inoculated intranasally with ceftazidime-resistant *P. aeruginosa* E2. In this study, an equimolar concentration of cilastatin was added to meropenem and imipenem to protect both carbapenems against hydrolysis by murine dehydropeptidase-1 (DHP-1). Mice were given 3 mg/kg of subcutaneous (s.c.) doripenem, meropenem, imipenem; or 10 mg/kg of s.c. ceftazidime 2.5 h after infection. Groups of mice were euthanized 0 to 12 h after infection, and lungs were removed for assessment of bacterial counts.

Pharmacokinetics was determined from a separate group of immunocompromised, infected mice. Blood was collected into heparinized syringes at 6 time points ranging from 0.83 to 2 h after s.c. administration of doripenem, meropenem-cilastatin, imipenem-cilastatin, or ceftazidime. Samples were analyzed by agar bioassay using *E. coli* 7437.

PROVISIONAL INTERPRETIVE CRITERIA

The initial identification of provisional breakpoints for doripenem was based on the evaluation of distributions of populations of microorganisms and on correlations with current breakpoints for imipenem and meropenem. It was recognized that these provisional breakpoints would have some temporary uses, but that establishment of final definitive breakpoints would require additional analyses and integration with the doripenem pharmacokinetic/pharmacodynamic properties, and correlation with clinical trial outcome results. In order to guide the testing of clinical isolates by setting provisional interpretive criteria, it was essential to determine preliminary quality control parameters and disk mass data. Further work included the completion of a definitive Tier II multicenter quality control MIC and disk study leading to QC ranges.

Susceptibility Test Quality Control Data

Local sites were allowed to perform disk susceptibility testing and bacterial identification as appropriate for patient care during the clinical trials. They were then instructed to send isolates to the Central Laboratory where bacterial identification and susceptibility testing were conducted, and results then compiled for use in this Microbiology Summary.

The table below (Table 37) contains the recommended quality control ranges determined by this Reviewer.

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Table 37. Acceptable Quality Control Ranges for Susceptibility Testing QC Organism Minimum Inhibitory Concentrations ($\mu\text{g/ml}$) Disk Diffusion (zone diameters in mm)

QC Isolate	ATCC #	Disk Diffusion Zone diameter (mm)	Minimum Inhibitory Concentration ($\mu\text{g/ml}$)
<i>E. coli</i>	25922	—	0.1-0.06
/	/	/	/
/	/	/	/
<i>P. aeruginosa</i>	27853	/	0.12-0.5
<i>S. pneumoniae</i>	49619	/	/
/	/	/	/
<i>B. fragilis</i>	25285	--	/
<i>B. thetaiotaomicron</i>	29741	--	0.12- —

Source: Table 32 and 33 and Appendices 3.1 and 3.2, this submission.

Quality Control Results From Clinical Trials

Quality control data from the central laboratory are presented in (Appendix 3, this submission). The data are presented as histograms showing the frequency with which individual MIC values or zone diameters for each of the QC organisms were recorded during the testing of clinical isolates from the cUTI, cIAI and NP trials. The data in these histograms are summarized here.

MIC QC testing gave acceptable results. All QC values were within the CLSI published range for *S. aureus* ATCC 29213 and *E. coli* ATCC 25922. For *P. aeruginosa* ATCC 27853 and *S. pneumoniae* ATCC 49619, < 5% of the MICs were out of range, with errors on the high side of the MIC distribution.

During the original testing of the clinical isolates at the central laboratory, using the CLSI published QC ranges for disk diffusion testing, only one of 32 zone diameters (3%) for *S. aureus* was out of range (2 mm smaller than the range). For *P. aeruginosa* ATCC 27853, three of four testing values (75%) were 1 or 2 mm lower than the CLSI recommended range. For *E. coli* ATCC 25922, 25% of the values (15 of 60 testing occasions) were out of range, with zone sizes generally 1 to 3 mm smaller. Testing of *S. pneumoniae* ATCC 49619 resulted in 4 of 12 zone sizes (33%) were out of range.

Further investigation into the cause of the failed QC results revealed that the quality control test failures which occurred at the lower end of the QC range began in 2005. It was determined by discussion with the central laboratory that the disks had been stored refrigerated rather than at -20°C or -70°C . Therefore, it was requested that the central laboratory conduct a comparison study testing the most recent disk lot available (— disks manufactured December 2005) and disks from the December 2003 lot that were used for testing clinical isolates from the first four doripenem trials (DORI-05, -

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06, -07, and -08). For this study, twenty inocula were prepared from each of four QC strains and the December 2003 (manufacture date) disk lot and the December 2005 (manufacture date) disk lot were tested. All QC results for the December 2005 disk lot were in range. There was a clear difference between the two lots of disks, with the 2003 disks providing smaller zone sizes, as expected based on the previous results that were seen from the QC performed during the testing of the clinical trial isolates. Interestingly, although the zone sizes were smaller with the 2003 disks compared to the 2005 disks, it was only for *P. aeruginosa* that results were out of range on the low side for the December 2003 disk lot. All the *E. coli* QC values were in range, although many of the results were on the lower end of the range upon retesting.

Based on these results, it was believed that the current lots of disks from the central laboratory (BD 2005) were acceptable and should be used to retest the clinical isolates from doripenem-treated subjects from the DORI-05, -06, -07 and -08 trials. All clinical isolates from subjects from the doripenem arms of the cIAI and cUTI trials that were tested in 2005 and 2006 were retested with the BD lot of disks manufactured in December 2005. Quality control values generated during retesting were in range. Quality control data that were generated in the central laboratory during retesting of the clinical isolates for disk zone sizes are presented in Appendix 3.3 (04 June 2007 submission). In addition, the figures below show the results of the comparison of disk results for the December 2003 lot of disks versus the December 2005 lot of disks.

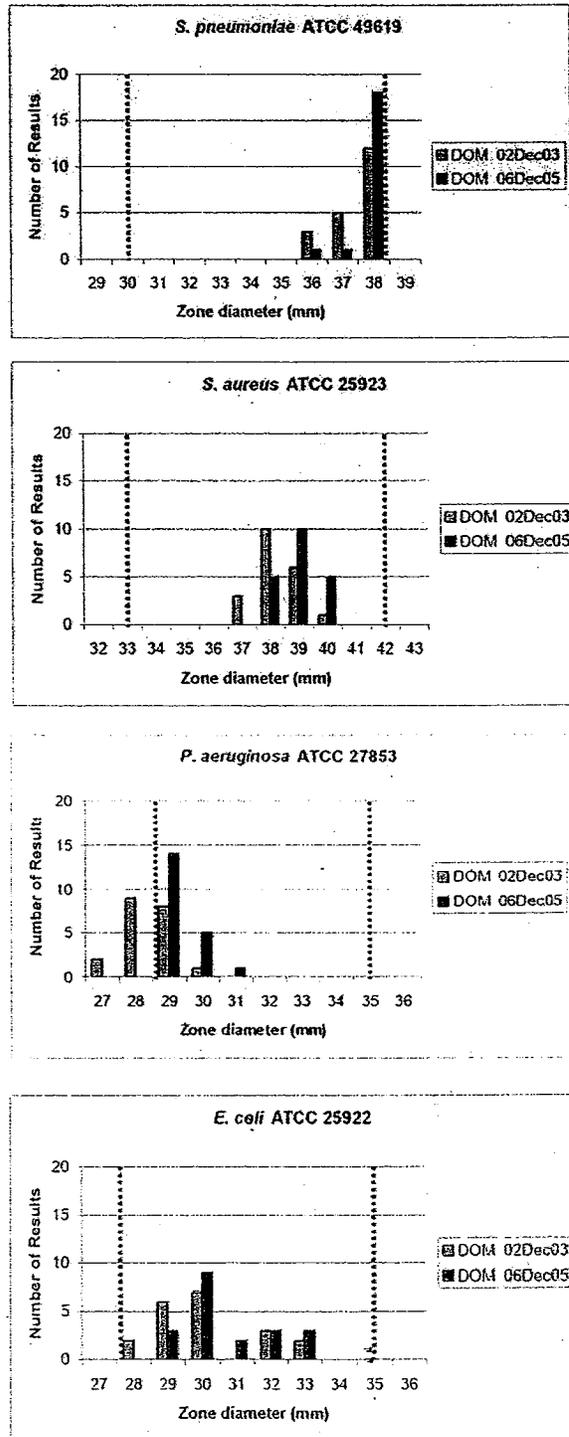
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Figure 6. Quality Control Disk Diffusion Values.



Source: Appendix 3.3, 04 June 2007 submission.