

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-821

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW

NDA 21-821

Date review completed: 15 Jun 05

Date company submitted: 15 Dec 04
Reviewer: Fred Marsik, Ph.D.

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Date assigned: 15 Dec 04

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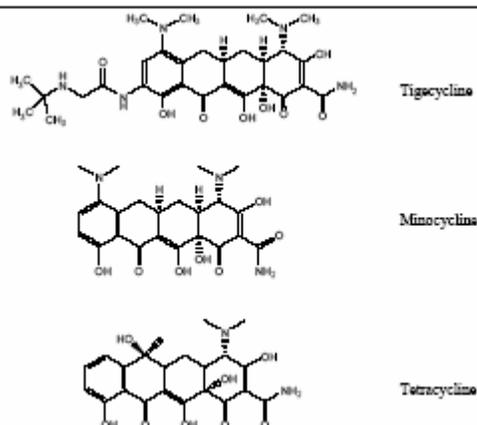
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DRUG PRODUCT NAME

Proprietary: TYGACIL™
Established name: GAR-936, Tigecycline
Code name/number: CL 346,635 and WAY 156,936
Chemical name: 9-t-butylglycylamido-minocycline
Molecular formula (empirical): C₂₉H₃₉N₅O₈
Molecular weight: 585.66

Figure 1.0-1: Molecular Structures of Tigecycline, Minocycline, and Tetracycline



DRUG CATEGORY: Antibacterial

PROPOSED INDICATIONS AND USAGE

Complicated skin and skin infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible

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and –resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes* and *Bacteroides fragilis*

Complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.

PROPOSED DOSAGE FORM, ROUTE OF ADMINISTRATION, DOSAGE, AND DURATION OF ADMINISTRATION

Dosage form: Liquid

Route of administration: IV

Dosage: loading dose of 100 mg tigecycline followed by 50 mg of IV tigecycline every 12 hours – IV infusion should be administered over approximately 30 to 60 minutes every 12 hours.

Duration of administration: The recommended duration of treatment with tigecycline for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days. The duration of therapy should be guided by the severity and site of the infection and the patient’s clinical and bacteriological progress.

DISPENSED: Rx

RELATED DOCUMENTS

IND (b) (4), IND 56,518

REMARKS

This will be a review of the clinical microbiology data submitted by the Applicant to support their desire to market this product for the treatment of “Complicated Skin and Skin Structure Infections” and “Complicated Intra-abdominal Infections”. In vitro susceptibility testing interpretive criteria will be determined for micro-broth dilution and disc diffusion testing against appropriate target pathogens.

CONCLUSION

Based on the tigecycline in vitro susceptibility test profile, the pharmacokinetics/pharmacodynamics of tigecycline and the bacteriological eradication rates and clinical cure rates the following interpretive criteria are proposed by the Agency for tigecycline.

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Table 2. Susceptibility Test Result Interpretive Criteria for Tigecycline

Pathogen	Minimum Inhibitory Concentrations (µg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	≤0.5 ^a	=	=	≥19	=	=
<i>Streptococcus</i> spp. other than <i>S. pneumoniae</i>	≤0.25 ^a	-	-	≥19	-	-
<i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only)	≤0.25 ^a	-	-	≥19	-	-
<i>Enterobacteriaceae</i> ^b	≤2	2-4	≥8	≥19	15-18	≤14
Anaerobes ^c	≤4	8	≥16	n/a	n/a	n/a

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

b. Tigecycline has decreased in vitro activity against *Morganella* spp, *Proteus* spp. and *Providencia* spp.

c. Agar dilution

The in vitro susceptibility test quality control parameters are indicated below.

Acceptable Quality Control Ranges for Susceptibility Testing

QC organism	Minimum Inhibitory Concentrations (µg/mL)	Disk Diffusion (zone diameters in mm)
<i>Staphylococcus aureus</i> ATCC 25923	Not Applicable	20-25
<i>Staphylococcus aureus</i> ATCC 29213	0.03-0.25	Not Applicable
<i>Escherichia coli</i> ATCC 25922	0.03-0.25	20-27
<i>Enterococcus faecalis</i> ATCC 29212	0.03-0.12	Not Applicable
<i>Bacteroides fragilis</i> ATCC 25285	0.12-1 ^d	Not Applicable
<i>Bacteroides thetaiotaomicron</i> ATCC 29741	0.5-2 ^d	Not Applicable
<i>Eubacterium lentum</i> ATCC 43055	0.06-0.5 ^d	Not Applicable

ATCC = American Type Culture Collection

d. Agar dilution

From a microbiology perspective the following organisms should be included in the indicated clinical indications for tigecycline.

Complicated skin and skin structure infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible strains only), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes* and *Bacteroides fragilis*.

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Complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates only); *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.

Second list of organisms

The organisms in the tigecycline package insert list would include the following:

Aerobic and facultative Gram-positive microorganisms

Enterococcus avium

Enterococcus casseliflavus

Enterococcus faecalis (vancomycin-resistant isolates)

Enterococcus faecium (vancomycin-susceptible and -resistant isolates)

Enterococcus gallinarum

Listeria monocytogenes

Staphylococcus epidermidis (methicillin-susceptible and -resistant isolates)

Staphylococcus haemolyticus

Aerobic and facultative Gram-negative microorganisms

Acinetobacter baumannii

Aeromonas hydrophila

Citrobacter koseri

Enterobacter aerogenes

Pasteurella multocida

Serratia marcescens

Anaerobic microorganisms

Bacteroides distasonis

Bacteroides ovatus

Peptostreptococcus spp.

Porphyromonas spp.

Prevotella spp.

Other microorganisms

Mycobacterium abscessus

Mycobacterium chelonae

Mycobacterium fortuitum

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From a microbiology perspective the following organisms would not appear in the second list for the reasons stated.

(b) (4)

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1. Because these organisms have recently been recognized as being associated with severe community-acquired skin infections and pneumonia and the disease is not well understood or the treatment for such infections clearly defined these organisms can only be included in the package insert after clinical studies have demonstrated that the antimicrobial, in this case tigecycline, can effectively treat the infection.

2. The following organisms will not be included in the second list because there is not sufficient clinical experience treating these infections with tigecycline or other antimicrobials.

(b) (4)

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(b) (4)



3. This organism is not relevant to the indications being sought.

4. While these organisms are members of the (b) (4) they are the cause of specific gastrointestinal illness and very rarely associated with cIAI.

5. This organism is not associated with cIAI. (b) (4)
Clinical studies are required to show that an antimicrobial can effectively treat the infection caused by this organism.

6. Tigecycline in vitro susceptibility data on less than 100 isolates provided by Applicant

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Following is the Agency's proposed section of the microbiology section of the tigecycline package insert.

6 Pages of Draft Labeling Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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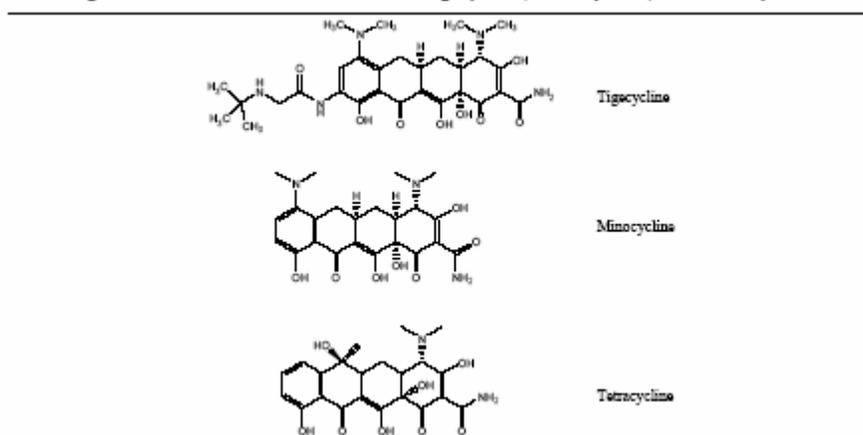
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<i>Staphylococcus</i> spp.	91
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EXECUTIVE SUMMARY

Tigecycline, also known as GAR-936, is an analogue of the tetracycline minocycline. Tigecycline belongs to the class of tetracycline called the glycylcyclines. It has been shown that certain substitutions at the 9 position of the tetracycline molecule restored activity against bacteria harboring resistance genes encoding either or both efflux and ribosomal protection. In the case of tigecycline 9-*t*-butylglycylamido was placed at the 9 position.

Figure 1.0-1: Molecular Structures of Tigecycline, Minocycline, and Tetracycline



Spectrum of Activity

Tigecycline has been shown to have activity against a wide spectrum of gram-positive and –negative aerobic, facultative anaerobes and anaerobes. This activity extends to those organisms harboring classical tetracycline resistance mechanisms.

Staphylococci are inhibited by 2 µg/mL of tigecycline or less. Against methicillin-susceptible *S. aureus* (MSSA) and MRSA (methicillin-resistant *S. aureus*), the tigecycline MIC₉₀ (MIC at which 90% of isolates were inhibited) is 0.12 and 0.25 µg/mL, respectively. Against methicillin-susceptible and resistant *Staphylococcus epidermidis*, tigecycline MIC₉₀ value is 0.5 µg/mL for both groups. The activity of tigecycline is consistent against penicillin-susceptible (PRSP), intermediate (PISP), and resistant (PRSP) *S. pneumoniae* isolates, with MIC₉₀ values of 0.06 µg/mL for all three categories of *S. pneumoniae*. The tigecycline MIC₉₀ values for beta-hemolytic streptococci, including *Streptococcus pyogenes*, and *Streptococcus agalactiae* are 0.06 µg/mL. Tigecycline is active against erythromycin-resistant *S. pneumoniae*, *S. pyogenes* and *S. agalactiae*. Against *Enterococcus faecalis* and *Enterococcus faecium*, MIC₉₀ value is 0.12 µg/mL for both vancomycin-susceptible (VS) and –resistant isolates (VR).

For members of the *Enterobacteriaceae* the tigecycline MIC_{90s} range from 0.5 µg/mL to 8 µg/mL with the highest MIC_{90s} being for *Morganella morganii* (4 µg/mL) and for *Proteus mirabilis* (8 µg/mL). Tigecycline does not exhibit significant in vitro activity

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against *Pseudomonas aeruginosa*, and demonstrates only moderate activity against *Proteus* species, *Morganella* species and *Providencia* species. The Applicant has not included either *M. morganii*, *P. mirabilis* or *Providencia* spp. in any of the indications that they are requesting in this submission.

In the case of *E. coli* the tigecycline MIC₉₀ for ESBL producing isolates and those not producing ESBLs is 0.5 µg/mL. For *K. pneumoniae* the tigecycline MIC₉₀ for non-ESBL producing isolates is 1 µg/mL and for the ESBL and AmpC producing *K. pneumoniae* isolates the tigecycline MIC_{90s} is 2 µg/mL. During clinical trials there was very limited experience treating infections caused by ESBL producing isolates or AmpC resistant isolates with tigecycline.

For anaerobic bacteria the tigecycline MIC_{90s} range from 0.25 µg/mL to 4 µg/mL, with *Bacteroides fragilis* having the higher MIC.

Mechanism of Action

Tetracycline acts by inhibiting protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl transfer RNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into the elongating peptide chains. Current evidence suggests that tigecycline binds more avidly to the ribosome such that the product of the *tet(M)* gene is unable to disrupt the tight glycylycylcline-ribosome bond or that the product of the *tet(M)* gene is unable to interact with the ribosome to allow protein synthesis to occur. The activity of tigecycline against isolates of bacteria that have efflux mechanisms of resistance likely results either from the inability of tigecycline to induce tetracycline efflux proteins or simply because the efflux pump is ineffective in transporting glycylycylclines out of the cell. In general tigecycline is considered bacteriostatic as are other tetracyclines.

Mechanism(s) of Resistance

Mutations in the interdomain loop region of the *tet(A)* tetracycline resistance gene that increases the efflux of minocycline and glycylycylclines has been reported in veterinary isolates of *Salmonella choleraesuis* and *Salmonella typhimurium* isolates. These mutations were shown to reduce susceptibility to the glycylycylcline class of antibiotics. This reduced susceptibility was more pronounced for the glycylycylclines DMG-MINO and DMG-DMOT than GAR-936 (TBG-MINO) (8 to 16 µg/mL vs. 2 µg/mL respectively). The novel *tet(A)* gene carries two mutations in the largest cytoplasmic loop of the efflux pump, which causes a double frameshift in codons 201, 202 and 203. This “interdomain region” of the efflux pump. Mutants of the *tet(B)* class with decreased susceptibility to the glycylycylclines have also been generated in vitro. It has been suggested that it will be the interdomain region of the pump that is likely to be the loci of future glycylycylcline resistance mutations as these compounds enter clinical use. How, commonly this resistance will occur as the glycylycylclines are used is unclear at this time.

Synergism/Antagonism

Synergy/antagonism studies showed that there were no consistent trends for synergy and no antagonism between tigecycline and a wide variety of antibiotic.

Tigecycline Pharmacodynamics

Information from the mouse thigh model of infection indicates that the time above some fraction of the MIC (e.g. 1.2) or the AUC correlates best with the efficacy of tigecycline.

Clinical Trial Results

Staphylococcus aureus (methicillin-susceptible and -resistant isolates)

Complicated skin and skin structure infections (cSSSI) and complicated intraabdominal infections (cIAI) clinical studies showed that there was an 87% (143/165) bacteriological eradication rate and clinical cure rate for *S. aureus* (methicillin-susceptible and -resistant isolates) with a tigecycline MIC of ≤ 0.5 $\mu\text{g/mL}$. There was minimal experience during clinical trials with using tigecycline to treat *S. aureus* infections where the tigecycline MIC for *S. aureus* (methicillin-susceptible and -resistant) > 0.25 $\mu\text{g/mL}$. The bacteriological eradication rate and clinical cure rate for *S. aureus* (methicillin-susceptible and -resistant) with a tigecycline MIC of ≤ 0.5 $\mu\text{g/mL}$ isolated from patients in the cIAI studies was 91% (29/32).

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Table 4.2.1.1-2: Microbiological Response and MIC Distribution for the ME Population from the Integrated cSSSI Trials for *S. aureus* Isolates

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative % of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.06	2/2	1.2	1.4	100	0
0.12	110/128 ^a	78.3	77.8	85.9	14.1
0.25	30/34	98.8	98.6	88.2	11.8
0.5	1/1	99.4	99.3	100	0
1	1/1	100.0	100	100	0
Total	144/166			86.7	13.3
ME-monomicrobial					
0.06	0	0	0	0	0
0.12	74/88	80.7	79.6	84.1	15.9
0.25	18/20	99.1	98.9	90.0	10.0
0.5	1/1	100	100	100	0
Total	93/109			85.3	14.7
ME-polymicrobial					
0.06	2/2	3.5	3.9	100	0
0.12	36/40	73.7	74.5	100	10.0
0.25	12/14	98.2	98.0	90.0	14.3
0.5	0	98.2	98.0	0	0
1	1/1	100	100	100	0
Total	51/57			89.5	10.5

^a The clinical response at 0.12 µg/mL was 113/128. For all other MICs the clinical response was the same as the microbiological response.

Table 4.2.1.1-3: Microbiological Response and MIC Distribution for the ME Population from the Integrated cIAI Trials for *S. aureus* Isolates

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total ^a	Cumulative % of total isolates	Cumulative % of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.12	17/17	53.1	58.6	100	0
0.25	11/14	96.9	96.6	78.6	21.4
0.5	1/1	100	100	100	0
Total	29/32			91.0	13.3

^a For all MICs the clinical response identical to the microbiological response.

Streptococci

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cSSSI clinical studies showed that there was a 94% (30/32) bacteriological eradication rate for *S. pyogenes* with a tigecycline MIC of ≤ 0.25 $\mu\text{g}/\text{mL}$ with a similar clinical cure rate. Therefore it is felt that it is appropriate to include in the package insert a MIC interpretive breakpoint for *S. pyogenes* of ≤ 0.25 $\mu\text{g}/\text{mL}$. The clinical experience with cSSSI infections due to *S. agalactiae* was too small to correlate an MIC with a meaningful bacteriologic eradication or clinical cure rate. For *S. anginosus*, with a tigecycline MIC of ≤ 0.25 $\mu\text{g}/\text{mL}$, there was 88 % (15/17) bacteriological eradication rate. The experience of treating infections due to other members of the *S. anginosus* grp. (*S. constellatus* and *S. intermedius*) was too limited to correlate a tigecycline MIC with a bacteriological eradication rate.

Table 4.2.1.2-2: Distribution of Individual *Streptococcus* Species Associated with Microbiological Eradication as Defined by the ME Population for Integrated cSSSI

Tigecycline Susceptibility MIC ($\mu\text{g}/\text{mL}$)	<i>S. pyogenes</i>	<i>S. agalactiae</i>	<i>S. anginosus</i>	<i>S. constellatus</i>	<i>S. intermedius</i>
0.008					1/1
0.015					
0.03			1/1		
0.06	22/23	3/3	6/8	1/2 ^a	
0.12	7/8 ^b	2/2	7/7		
0.25	1/1	2/3 ^c	1/1		
0.5					
Total	30/32	7/8	15/17	1/2	1/1

^a The clinical response for *S. constellatus* at 0.06 $\mu\text{g}/\text{mL}$ was 0/2.

^b The clinical response for *S. pyogenes* at 0.12 $\mu\text{g}/\text{mL}$ was 8/8.

^c The clinical response for *S. agalactiae* at 0.25 $\mu\text{g}/\text{mL}$ was 3/3.

cIAI clinical studies showed that for the *S. anginosus* group of streptococci a tigecycline MIC of ≤ 0.25 $\mu\text{g}/\text{mL}$ correlated with a 86% (102/118) bacteriological eradication rate with a similar clinical cure rate.

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Table 4.2.1.2-4: Microbiological Response and MIC Distribution for the ME population from the cIAI Trials for *Streptococcus anginosus* group.

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative # of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.008	1/1	0.8	1.0	100	0
0.015	2/2	2.5	2.9	100	0
0.03	4/4 ^a	5.9	6.9	100	0
0.06	79/91 ^b	83.1	84.3	86.8	13.2
0.12	15/18	98.3	99.0	83.3	16.7
0.25	1/2	100	100	50	50
Total	102/118			86.4	13.6

^a The clinical response at 0.03 µg/mL was 3/4.

^b The clinical response at 0.06 µg/mL was 78/91. For all other MICs the clinical response was identical the microbiological response.

Enterococci

The Applicant only presented clinical data for *Enterococcus faecalis* (vancomycin-susceptible). This is the only *Enterococcus* spp. that they are asking for in the indications and usage section of the package insert. In vitro the tigecycline MIC₉₀ ranges from 0.12 µg/mL to 0.25µg/mL for both vancomycin-resistant *E. faecalis* and vancomycin-susceptible and –resistant *Enterococcus faecium*.

cSSSI clinical studies showed that for vancomycin-susceptible *E. faecalis* a tigecycline MIC of ≤0.25 µg/mL correlated with an 88% (14/16) bacteriological eradication rate and a 75% (12/14) clinical cure rate.

cIAI clinical studies showed that for vancomycin-susceptible *E. faecalis* a tigecycline MIC of ≤0.25 µg/mL correlated with a 81% (26/32) bacteriological eradication rate and a similar clinical cure rate. For vancomycin-susceptible *E. faecalis* a tigecycline MIC of ≤0.25 µg/mL correlated with a bacteriological eradication rate of 81% (26/32) with a similar clinical cure rate.

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Table 4.2.1.3-3: Microbiological Response and MIC Distribution for the ME Population from the Integrated cSSSI Trials for *E. faecalis* Isolates

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative % of isolates associated with microbiological eradications	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.12	10/12 ^a	75	71.4	83.3	16.7
0.25	4/4 ^b	100	100	100	0
Total	14/16			87.5	12.5
ME-polymicrobial					
0.12	9/11	78.6	75	81.8	18.2
0.25	3/3	100	100	100	0
Total	12/14			85.7	14.3

^a The clinical response at 0.12 µg/mL was 9/12.

^b The clinical response at 0.25 µg/mL was 3/4. For all other MICs the clinical response was identical to the microbiological response.

Table 4.2.1.3-2: Microbiological Response and MIC Distribution for the ME Population from the Integrated cIAI Trials for *E. faecalis* Isolates

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative % of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.06	2/2	6.3	7.7	100	0
0.12	13/17	59.4	57.7	76.5	23.5
0.25	11/13 ^a	100	100	84.6	15.4
Total	26/32			81.3	18.8

^a The clinical response at 0.25 µg/mL was 10/13. For all other MICs the clinical response was identical to the microbiological response.

Enterobacteriaceae

The Applicant only proved clinical study data for the following members of the *Enterobacteriaceae*: *Escherichia coli*, *Enterobacter cloacae*, *Citrobacter freundii*, *Klebsiella oxytoca* and *Klebsiella pneumoniae*. The Applicant is asking for the inclusion of *E. coli* in cSSSI indication and all of the indicated organisms in the cIAI indication. Tigecycline does not have good in vitro activity against all *Enterobacteriaceae* (e.g. *Morganella* spp., *Proteus* spp., and *Providencia* spp.).

During the clinical trials (Phase 2 and 3) there were incidences of the development of decreased susceptibility (MIC ≥4 µg/mL) to tigecycline while the patient was receiving tigecycline. In total there were six organisms from five patients that had decreased susceptibility. All of the isolates were documented to be identical to the baseline isolate by ribotyping. There were two patients with *K. pneumoniae*, and one patient each that had *E. aerogenes*, *Acinetobacter calcoaceticus/baumanni*, and *M. morganii*. In addition,

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there was one patient that had an *E. coli* isolate for which the tigecycline MIC increased from 0.5 to 2 µg/mL.

cSSSI clinical studies showed that for all infections there was a 83% (24/29) correlation with bacteriological eradication with a similar clinical cure rate for *E. coli* with a tigecycline MIC of ≤ 1 µg/mL. During cSSSI clinical trials there was very limited experience with *E. coli* that had a tigecycline MIC >0.25 µg/mL.

Table 4.2.1.4-5: Microbiological Response and MIC Distribution for the ME Population from the Integrated cSSSI Trials for *E. coli* Isolates

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response		Cumulative % of isolates		
	N ns/N total	Cumulative % of total isolates	associated with eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all					
0.12	5/6	20.7	85.9	88.3	16.7
0.25	14/16 ^a	75.9	88.2	87.5	12.5
0.5	4/6	96.6	66.7	66.7	33.3
1	1/1	100	100	100	0
Total	24/29			82.8	17.2
ME-monomicrobial					
0.12	3/4	40	37.5	75	25
0.25	2/2	60	62.5	100	0
0.5	2/3	90	87.5	66.7	33.3
1.0	1/1	100	100	100	0
Total	8/10			80.0	20
ME-polymicrobial					
0.12	2/2	10.5	12.5	100	0
0.25	12/14	84.2	87.5	85.7	14.3
0.5	2/3	100	100	66.7	33.3
Total	16/19			84.2	15.8

^a The clinical response at 0.25 µg/mL was 15/16. For all other MICs the clinical response was identical to the microbiological response.

cIAI clinical studies showed that there was a 86% (370/428) correlation of a tigecycline MIC of ≤2 µg/mL with bacteriological eradication for infections caused by *C. freundii*, *E. coli*, *E. cloacae* and *K. pneumoniae* as sole agents of infection. For all infections (monomicrobial + polymicrobial) involving all *Enterobacteriaceae* isolated during cIAI clinical trials the bacteriological eradication rate where the tigecycline MIC of ≤2 µg/mL was 86% (370/428). There was a similar clinical cure rate.

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Table 4.2.1.4-3: Distribution of Individual *Enterobacteriaceae* Associated with Microbiological Eradication as Defined by the ME Population for Integrated cIAI

Tigecycline Susceptibility MIC ($\mu\text{g}/\text{mL}$)	<i>C. freundii</i>	<i>E. cloacae</i>	<i>K. oxytoca</i>	<i>E. coli</i>	<i>K. pneumoniae</i>
0.06				2/3	
0.12				31/37 ^a	
0.25	3/3		7/7	188/217 ^b	1/1
0.5	5/7	9/9	12/13	54/63	23/16
1	2/4	5/7		5/5	16/19
2	2/2				5/5
4					1/1
Total	12/16	14/16	19/20	280/325	46/52

^a The clinical response for *E. coli* at 0.12 $\mu\text{g}/\text{mL}$ was 30/37.

^b The clinical response for *E. coli* at 0.25 $\mu\text{g}/\text{mL}$ was 187/217.

Table 4.2.1.4-2: Microbiological Response and MIC Distribution for the ME Population from the Integrated cIAI Trials for *Enterobacteriaceae* Isolates

Tigecycline Susceptibility MIC ($\mu\text{g}/\text{mL}$)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative% of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.06	2/3	0.7	0.5	66.7	33.3
0.12	31/37 ^a	9.3	8.9	83.8	16.2
0.25	199/228 ^b	62.5	62.5	87.3	12.7
0.5	103/118	90.0	90.3	87.3	12.7
1	28/35	98.1	97.8	80.0	20.0
2	7/7	99.8	99.7	100	0
4	1/1	100	100	100	0
Total	371/429		100	86.5	13.5
ME-monomicrobial					
0.06	0	0	0	0	0
0.12	13/14	12.0	12.0	92.9	7.1
0.25	66/70	71.8	73.1	94.3	5.7
0.5	23/25	93.2	94.4	92.0	8.0
1	4/6	98.3	98.1	66.7	33.3
2	2/2	100	100	100	7.7
Total	108/117			92.3	

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Table 4.2.1.4-2: Microbiological Response and MIC Distribution for the ME Population from the Integrated cIAI Trials for *Enterobacteriaceae* Isolates

Tigecycline Susceptibility MIC (µg/mL)	Microbiological responseN eradications/N total	Cumulative % of total isolates	Cumulative% of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-polymicrobial					
0.06	2/3	1.0	0.8	66.7	33.3
0.12	18/23	8.3	7.6	78.3	21.7
0.25	133/158	59.0	58.2	84.2	15.8
0.5	80/93	88.8	88.6	86.0	14.0
1	24/29	98.1	97.7	82.8	17.2
2	5/5	99.7	99.6	100	0
4	1/1	100	100	100	0
Total	263/312			84.3	

Clinical response is given for each pathogen in Table 4.2.1.4-3.

Anaerobes

The Applicant is proposing that (b) (4) be included as the target pathogen in the cSSI indication. In the cIAI indication they are proposing that the following anaerobic bacteria be included as target pathogens: *B. fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.

(b) (4)

The cIAI clinical trials noted below provide some additional information on the efficacy of tigecycline against *B. fragilis*. cIAI clinical studies showed that there was a bacteriological eradication rate of 78% (65/83) when the tigecycline MIC was ≤ 4 µg/mL for *B. fragilis*.

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(b) (4)

cIAI clinical studies showed that there was a bacteriological eradication rate of 84% (158/189) when the tigecycline MIC was ≤ 4 $\mu\text{g}/\text{mL}$ for *B. fragilis*, *B. thetaiotaomicron*, *B. uniformis*, *B. vulgatus*, *C. perfringens*, and *P. micros*. The overall clinical cure rate was similar to the bacteriological eradication rate for all the mentioned organisms.

Table 4.2.1.5-3: Distribution of Individual Anaerobes Associated with Microbiological Eradication as Defined by the ME Population for Integrated cIAI

Tigecycline Susceptibility MIC ($\mu\text{g}/\text{mL}$)	<i>B. fragilis</i>	<i>B. thetaiotaomicron</i>	<i>B. vulgatus</i>	<i>B. uniformis</i>	<i>C. perfringens</i>	<i>P. micros</i>
0.06			5/5	2/3	6/6	12/16
0.12	2/2	5/8	2/2	4/4	4/5	1/1
0.25	14/16	6/7	3/3	3/4 ^d	2/2	
0.5	19/24	10/10	3/5	4/4	2/2	
1	21/31 ^a	8/8			2/2	
2	7/8	4/4 ^e			2/2	
4	2/2	1/1	1/1	1/1 ^e		
8	2/2	1/1				
16	2/2 ^b	2/2		1/1 ^f		
Total	69/87	37/41	14/16	15/17	18/19	13/17

^a The clinical response for *B. fragilis* at 1.0 $\mu\text{g}/\text{mL}$ was 20/31.

^b The clinical response for *B. fragilis* at 16 $\mu\text{g}/\text{mL}$ was 1/2.

^c The clinical response for *B. thetaiotaomicron* at 2.0 $\mu\text{g}/\text{mL}$ was 3/4.

^d The clinical response for *B. uniformis* at 0.25 $\mu\text{g}/\text{mL}$ was 2/4.

^e The clinical response for *B. uniformis* at 4.0 $\mu\text{g}/\text{mL}$ was 0/1.

^f The clinical response for *B. uniformis* at 16.0 $\mu\text{g}/\text{mL}$ was 0/1.

In Vitro Susceptibility Testing

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Disc diffusion and micro broth dilution susceptibility testing of bacteria against tigecycline is done by currently recognized Clinical and Laboratory Standard Institute (CLSI) methods. Broth dilution susceptibility testing requires the use of fresh media because tigecycline can be oxidatively degraded. Disc diffusion testing is done with a 15 µg disc. Susceptibility testing of anaerobic bacteria is done by agar dilution not by micro broth dilution.

In vitro susceptibility testing interpretive criteria

The Applicant is proposing the following in vitro susceptibility test interpretive criteria.

Table 4.2.1-1: Proposed Interpretive Criteria For Tigecycline						
Grouping	MIC (µg/mL)			Zone (mm)		
	S	I	R	S	I	R
<i>Streptococcus</i> spp. not <i>S. pneumoniae</i>	(b) (4)	-	-	≥19	-	-
						(b) (4)
Enterobacteriaceae	≤2	4	≥8	≥19	15-18	≤14
Anaerobes	≤4	8	(b) (4)	NA	NA	NA

Based on a review of the tigecycline in vitro susceptibility test data for preclinical and clinical isolates, its pharmacokinetics/pharmacodynamics parameters, the bacteriological eradication and clinical outcome results from the cSSSI and cIAI studies, and correlation of MIC test results with agar disc diffusion test results the Agency is proposing the following in vitro susceptibility test interpretive criteria. Because tigecycline does not have good activity against all *Enterobacteriaceae* (e.g. *Morganella* spp., *Proteus* spp., *Providencia* spp.) this is noted in a footnote to susceptibility test interpretive criteria for *Enterobacteriaceae*. Intermediate and resistant interpretive criteria are not noted for *S. aureus*, *Streptococcus* species other than *Streptococcus pneumoniae* and *E. faecalis* because there is none or very limited clinical experience with isolates of these organisms above the proposed MIC indicating susceptibility to tigecycline.

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Susceptibility Test Result Interpretive Criteria for Tigecycline

Pathogen	Minimum Inhibitory Concentrations (µg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	≤0.5 ^a	-	-	≥19		
<i>Streptococcus</i> spp. other than <i>Streptococcus pneumoniae</i>	≤0.25 ^a	-	-	≥19	-	-
<i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only)	≤0.25 ^a	=	=	≥19		
<i>Enterobacteriaceae</i> ^b	≤2	4	≥8	≥19	15-18	≤14
Anaerobes ^c	≤4	8	≥16	n/a	n/a	n/a

- a. The current absence of resistant isolates precludes defining any results other than “Susceptible”. Isolates yielding MIC results suggestive of a “Nonsusceptible” category should be submitted to a reference laboratory for further testing.
- b. Tigecycline has reduced activity against *Morganella* spp., *Proteus* spp. and *Providencia* spp.
- c. Agar dilution

Clinical Indications and Usage

From a clinical microbiology perspective the target pathogens that should be included for the two proposed indications are indicated below.

Complicated skin and skin structure infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible strains only), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes* and *Bacteroides fragilis*.

Complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates only); *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.

Organisms proposed for second list by the Agency

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In order for organisms to be included in the second list of the microbiology section of a package insert certain criteria must be met. These criteria are: 1) they must be relevant to the indications for which the drug is proposed, 2) the MIC₉₀ for the organisms must be within the therapeutic concentration of the antimicrobial that can be achieved with the proposed dosing regimen. The organisms being proposed for the second list of the tigecycline package insert by the Agency are provided below. The organisms that are not felt appropriate for the second list are indicated and the reason for their exclusion is provided

The organisms in the tigecycline package insert list would include the following:

Aerobic and facultative Gram-positive microorganisms

Enterococcus avium

Enterococcus casseliflavus

Enterococcus faecalis (vancomycin-resistant isolates)

Enterococcus faecium (vancomycin-susceptible and -resistant isolates)

Enterococcus gallinarum

Listeria monocytogenes

Staphylococcus epidermidis (methicillin-susceptible and -resistant isolates)

Aerobic and facultative Gram-negative microorganisms

Acinetobacter baumannii

Aeromonas hydrophila

Citrobacter koseri

Enterobacter aerogenes

Pasteurella multocida

Serratia marcescens

Stenotrophomonas maltophilia

Anaerobic microorganisms

Bacteroides distasonis

Bacteroides ovatus

Peptostreptococcus spp.

Porphyromonas spp.

Prevotella spp.

Other microorganisms

Mycobacterium abscessus

Mycobacterium chelonae

Mycobacterium fortuitum

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From a microbiology perspective the following organisms would not appear in the second list for the reasons stated.

(b) (4)

[Redacted]

[Redacted]

1. Because these organisms have recently been recognized as being associated with severe community-acquired skin infections and pneumonia and the disease is not well understood or the treatment for such infections clearly defined these organisms can only be included in the package insert after clinical studies have demonstrated that the antimicrobial, in this case tigecycline, can effectively treat the infection.

2. The following organisms will not be included in the second list because there is not sufficient clinical experience treating these infections with tigecycline or other antimicrobials. These organisms also represent a special set of bacteria that contain specific resistance mechanisms.

(b) (4)

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(b) (4)



(b) (4)



(b) (4)



3. This organism is not relevant to the indications being sought.

4. While these organisms are members of the (b) (4) they are the cause of specific gastrointestinal illness and very rarely associated with cIAI.

5. This organism is not associated with cIAI. It produces a toxin related infection of the gastrointestinal tract. Clinical studies are required to show that an antimicrobial can effectively treat the infection caused by this organism.

6. Tigecycline in vitro susceptibility data on less than 100 isolates provided by Applicant

AGENCY'S PROPOSED MICROBIOLOGY SECTION OF THE TIGECYCLINE PACKAGE INSERT

(b) (4)

[Redacted]

(b) (4)

[Redacted]

[Redacted]

(b) (4)

[Redacted]

[Redacted]

INTRODUCTION

Tigecycline, also known as GAR-936, is an analogue of the tetracycline minocycline. Tigecycline belongs to the class of tetracyclines called the glycylcyclines. It has been shown that certain substitutions at the 9 position of the tetracycline molecule restored activity against bacteria harboring resistance genes encoding either or both efflux and ribosomal protection. In the case of tigecycline 9-*t*-butylglycylamido was placed at the 9 position.

IN VITRO

Tigecycline has been shown to have activity against a wide spectrum of gram-positive and –negative aerobic, facultative anaerobic and anaerobic bacteria.

Spectrum of Activity

Table 1 shows the MIC_{50s} and MIC_{90s} of tigecycline published in the literature against the pathogens included in the clinical indications that the Applicant is requesting (1,2,3). As can be seen the tigecycline MICs are low and below the concentration of tigecycline that can be achieved in the blood (See Pharmacokinetics portion of review). Tigecycline does not have significant in vitro activity against *Pseudomonas aeruginosa*, and demonstrates only moderate activity against *Proteus* species, *Morganella* species and *Providencia* species.

Table 1. In vitro activity of tigecycline against various bacteria.

Organism	Number of Isolates	MIC ₅₀ µg/mL	MIC ₉₀ µg/mL	MIC Range µg/mL
<i>Staphylococcus aureus</i>				
Methicillin-susceptible	40	0.25	0.25	0.12 - 0.25
Methicillin-resistant	40	0.25	0.25	≤0.06 - 0.5
[Redacted] (b) (4)	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]

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(b) (4)				
<i>Citrobacter freundii</i>	20	0.5	2	0.25 - 4
(b) (4)				
<i>Escherichia coli</i>	40	0.25	0.25	0.12 - 0.25
<i>Klebsiella oxytoca</i>	10	0.25	1	0.25 - 1
<i>Klebsiella pneumoniae</i>	20	0.5	1	0.5 - 4
(b) (4)				
<i>Bacteroides fragilis</i>	30	2	16	1 - 32
(b) (4)				

Table 2 shows the MICs of tigecycline against a variety of clinical isolates collected between 1997 – 2004 (data obtained from Wyeth Laboratories). The MICs were determined using NCCLS [now known as the Clinical and Laboratory Standards Institute (CLSI)] methods for in vitro susceptibility testing (4).

All of the staphylococci tested were inhibited by 2 µg/mL of tigecycline or less. Against methicillin-susceptible *S. aureus* (MSSA) and MRSA (methicillin-resistant *S. aureus* – including community-acquired isolates), the tigecycline MIC₉₀ (MIC at which 90% of isolates were inhibited) was 0.12 and 0.25 µg/mL, respectively. Against methicillin-susceptible and resistant *Staphylococcus epidermidis*, tigecycline MIC₉₀ values were 0.5 µg/mL, for both groups. The activity of tigecycline was consistent against penicillin-susceptible (PRSP), intermediate (PISP), and resistant (PRSP) *S. pneumoniae* isolates, with MIC₉₀ values of 0.06 µg/mL for all three categories of *S. pneumoniae*. The

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tigecycline MIC₉₀ values for beta-hemolytic streptococci, including *Streptococcus pyogenes*, and *Streptococcus agalactiae*, were 0.06 µg/mL. Against *Enterococcus faecalis* and *Enterococcus faecium*, MIC₉₀ values were 0.12 µg/mL for both vancomycin-susceptible (VS) and –resistant isolates (VR).

For members of the *Enterobacteriaceae* in Table 2 the tigecycline MIC_{90s} ranged from 0.5 µg/mL to 8 µg/mL with the highest MIC_{90s} being for *Morganella morganii* (4 µg/mL) and for *Proteus mirabilis* (8 µg/mL). It should be noted that the Applicant has not included either *M. morganii* or *P. mirabilis* in any of the indications that they are requesting in this submission. In the case of *E. coli* the tigecycline MIC_{90s} for ESBL producing isolates and those not producing ESBLs were 0.5 µg/mL while for *K. pneumoniae* the tigecycline MIC₉₀ for non-ESBL producing isolates is 1 µg/mL and for the ESBL and AmpC producing *K. pneumoniae* isolates the tigecycline MIC_{90s} were 2 µg/mL.

For the anaerobic bacteria noted in Table 2 the tigecycline MIC_{90s} ranges from 0.25 µg/mL to 4 µg/mL.

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Table 2.

Table 1
In vitro activities of tigecycline against clinical isolates obtained 1997–2004 [15]

Organisms	Number of isolates	MIC (mg/L)		
		Range	50%	90%
Gram-positive aerobic pathogens				
<i>Staphylococcus aureus</i>				
Methicillin-susceptible	160	0.03–0.25	0.12	0.12
Methicillin-resistant	170	0.03–2	0.12	0.25
Community-acquired methicillin-resistant	10	0.12–0.25	0.12	0.25
Glycopeptide-intermediate	19	0.06–1	0.12	0.25
<i>Staphylococcus epidermidis</i>				
Methicillin-susceptible	159	0.03–2	0.12	0.5
Methicillin-resistant	155	0.03–1	0.12	0.5
<i>Staphylococcus haemolyticus</i>				
	166	≤0.016–2	0.25	0.5
<i>Streptococcus pneumoniae</i>				
Penicillin-susceptible	176	≤0.03–0.12	≤0.03	0.06
Penicillin-intermediate	305	≤0.03–0.03	≤0.03	0.06
Penicillin-resistant	270	≤0.03–0.25	≤0.03	0.06
<i>Streptococcus pyogenes</i>				
	176	≤0.03–0.06	≤0.03	0.06
<i>Streptococcus agalactiae</i>				
	115	≤0.03–0.06	≤0.03	0.06
<i>Enterococcus faecalis</i>				
Vancomycin-susceptible	159	0.03–0.25	0.06	0.12
Vancomycin-resistant	147	≤0.016–0.5	0.06	0.12
<i>Enterococcus faecium</i>				
Vancomycin-susceptible	171	≤0.03–0.25	0.06	0.12
Vancomycin-resistant	155	≤0.03–0.25	≤0.03	0.12
Gram-negative aerobic pathogens				
<i>Citrobacter freundii</i>				
	160	≤0.06–8	0.25	0.5
<i>Enterobacter aerogenes</i>				
	161	≤0.06–4	0.25	1
<i>Enterobacter cloacae</i>				
	160	0.25–8	0.5	0.5
<i>Escherichia coli</i>				
Non-ESBL producing	208	0.06–1	0.12	0.5
ESBL producing	170	0.06–4	0.25	0.5
<i>Klebsiella pneumoniae</i>				
Non-ESBL, non-AmpC producing	180	0.25–4	0.5	1
ESBL producing	171	0.12–4	0.5	2
AmpC producing	89	0.25–4	1	2
<i>Klebsiella oxytoca</i>				
	140	0.12–2	0.25	0.5
<i>Morganella morganii</i>				
	145	0.12–8	1	4
<i>Proteus mirabilis</i>				
	160	0.5–16	4	8
<i>Serratia marcescens</i>				
	160	0.25–8	1	2
<i>Salmonella enterica</i> ser Enteritidis				
	229	0.12–2	0.5	1
<i>Shigella sonnei</i>				
	274	0.06–1	0.25	0.5
<i>Pseudomonas aeruginosa</i>				
	160	0.25–32	8	16
<i>Acinetobacter baumannii</i>				
	158	0.03–4	0.5	2
<i>Aeromonas hydrophila</i>				
	142	0.06–1	0.25	0.5
<i>Burkholderia cepacia</i>				
	183	0.06–32	4	16
<i>Stenotrophomonas maltophilia</i>				
	160	0.06–16	0.5	2
<i>Haemophilus influenzae</i>				
	204	0.06–1	0.25	0.5
<i>Haemophilus parainfluenzae</i>				
	157	0.06–2	0.5	1
<i>Moraxella catarrhalis</i>				
	240	≤0.03–0.25	0.06	0.12
<i>Pasteurella multocida</i>				
	126	≤0.015–0.25	0.03	0.12
Anaerobes				
<i>Bacteroides fragilis</i>				
	425	0.015–32	1	4
<i>Prevotella</i> spp.				
	81	0.015–1	0.12	0.5
<i>Clostridium difficile</i>				
	63	≤0.06–0.5	0.25	0.5
<i>Clostridium perfringens</i>				
	70	0.03–4	0.06	0.5
<i>Eubacterium lentum</i>				
	30	≤0.06–1	0.25	0.25
<i>Peptostreptococcus</i> spp.				
	99	0.015–0.25	0.06	0.25

Susceptibility testing with tigecycline in broth requires the use of fresh media that is less than 12 hours old at the time that the drug is diluted in the broth media. The reason for this is that tigecycline is susceptible to oxidative degradation. MIC tests for aerobic organisms in fresh media are referred to by the Applicant as the “reference method” for

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tigecycline. This methodology has been approved for use by the Clinical Laboratory and Standards Institute (formerly known as the National Committee for Clinical Laboratory Standards) (5,6). The Applicant in this submission has provided in subsection 1.6.1 of section 2.7.2.4 (Special Studies) of this submission the rationale and data to support this requirement for in vitro susceptibility testing in broth media. The key to this caveat is the need to add the drug to broth media that is <12 hours old. If the drug is added to broth media <12 hours old and the broth media with the drug is immediately frozen and the plates used for susceptibility testing with 12 hours of use there is no effect on the MIC of aerobic bacteria. The Applicant in subsection 1.6.1 of section 2.7.2.4 (Special Studies) of this submission has provided experimental data to support this fact. Only the testing of facultative bacteria is effected since anaerobic testing is done under anaerobic conditions and thus there is no oxygen to oxidatively degrade the tigecycline.

In this submission the Applicant has provided MIC data for a variety of aerobic and anaerobic gram-positive and -negative bacteria (subsection 1.1.3 of section 2.7.2.4 – Special Studies). Table 3 contains the MIC data for the bacteria that the Applicant is requesting for inclusion in the Indications and Usage section of the package insert. The Applicant is not requesting the inclusion of *E. coli* producing ESBLs or *K. pneumoniae* producing AmpC or ESBLs. This data is provided for information purposes only. The in vitro susceptibility testing of the facultative bacteria in Table 3 was done by the “reference method” meaning that the testing was done within 12 hours of adding the tigecycline to the broth media.

Table 3. In vitro susceptibility of various bacteria listed in the proposed label for for tigecycline using the "reference" broth dilution method for facultative organisms

<u>Organism</u>	<u>Number of isolates</u>	<u>MIC₅₀ µg/mL</u>	<u>MIC₉₀ µg/mL</u>	<u>Range µg/mL</u>
<u>Facultative Bacteria</u>				
<i>Enterococcus faecalis</i> Vancomycin susceptible	159	0.06	0.12	0.03 - 0.25
(b) (4)				
<i>Staphylococcus aureus</i> methicillin susceptible	160	0.12	0.12	0.03 - 0.25
<i>S. aureus</i> methicillin resistant	165	0.12	0.12	0.03 - 2
<i>Streptococcus agalactiae</i>	115	≤0.03	0.06	≤0.03 - 0.06
<i>Streptococcus pyogenes</i>	176	≤0.03	0.06	≤0.03 - 0.06

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<i>Citrobacter freundii</i>	160	0.25	0.5	0.03 - 8
<i>Enterobacter cloacae</i>	160	0.5	0.5	0.25 - 8
<i>Escherichia coli</i>	208	0.12	0.5	0.06 - 1
<i>Klebsiella oxytoca</i>	140	0.25	0.5	0.12 - 2
<i>Klebsiella pneumoniae</i>	180	0.5	1	0.25 - 4
<u>Anaerobic Bacteria</u>				
<i>Bacteroides fragilis</i>	905	2	8	0.01 - 32
<i>Bacteroides</i>				
<i>thetaiotaomicron</i>	315	2	8	0.12 - 32
<i>Bacteroides uniformis</i>	57	1	4	0.06 - 8
<i>Bacteroides vulgatus</i>	120	1	4	0.12 - 8
<i>Clostridium perfringens</i>	50	0.12	0.5	0.03 - 4
<i>Peptostreptococcus</i>				
<i>micros</i>	14	0.03	0.5	0.016 - 0.25

Table 4 contains the in vitro MIC data for a variety of bacteria that the Applicant is requesting to be included in “second” list of bacteria in the “Microbiology” section of the Package insert. The MICs for facultative bacteria in Table 4 were determined using the “reference method”. The organisms in the second list in the “Microbiology” portion of the package insert are placed there on the basis that there is in vitro susceptibility data for at least 100 isolates of bacteria that are pertinent to the indications being sought and that the MIC₉₀ of each organism is at an concentration of the drug that can be achieved in the blood by routine dosing of the drug. The Applicant is requesting that (b) (4) included in the second list. Because this organism is not relevant to either the “Complicated Skin and Skin Structure Infections” or the “Complicated Intra-abdominal Infection” indication it will not be allowed in the second list. The Applicant is also requesting that a (b) (4) be included in the second list. Because these organisms also are not relevant to either of the indications being requested by the Applicant they will not be allowed in the second list. The following organisms are also being requested by the Applicant to be included in the second list but will not be allowed because there is MIC data on fewer than 100 isolates: (b) (4) will not be allowed in the second list of the package insert because they cause a different type of skin infection than do other bacteria and they are intracellular pathogens. Well controlled clinical studies where tigecycline is used to treat infections due to these organisms would need to be

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conducted before they were incorporated into the package insert for tigecycline or any other antimicrobial.



Table 4. In vitro susceptibility of various bacteria listed in the proposed label for the second list in the microbiology section of the package insert using the "reference method" for in vitro susceptibility testing for facultative bacteria

<u>Organism</u>	<u>Number of isolates</u>	<u>MIC₅₀ µg/mL</u>	<u>MIC₉₀ µg/mL</u>	<u>Range µg/mL</u>
<u>Facultative Bacteria</u>				
<i>Enterococcus avium</i>	140	0.06	0.12	≤0.016 - 0.25
<i>Enterococcus casseliflavus</i>	100	0.06	0.12	0.03 - 0.25
<i>Enterococcus faecalis</i> vancomycin-resistant	147	0.06	0.12	≤0.016 - 0.5
<i>Enterococcus faecium</i> vancomycin-susceptible	171	0.06	0.12	≤0.03 - 0.25
<i>Enterococcus faecium</i> vancomycin-resistant	155	≤0.03	0.12	≤0.03 - 0.25
<i>Enterococcus gallinarum</i>	164	0.06	0.12	≤0.03 - 0.25
<i>Listeria monocytogenes</i>	220	0.06	0.12	≤0.03 - 0.12
<i>Staphylococcus epidermidis</i> methicillin-susceptible	159	0.12	0.25	0.03 - 0.12
<i>S. epidermidis</i> methicillin-resistant	155	0.12	0.5	0.03 - 1
<i>Staphylococcus haemolyticus</i>	166	0.25	0.5	≤0.016 - 2
<i>Acinetobacter baumannii</i>	158	0.5	2	0.03 - 4
<i>Aeromonas hydrophilia</i>	142	0.25	0.5	0.06 - 1
<i>Citrobacter koseri</i>	175	0.25	0.5	0.03 - 8

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(b) (4)				
<i>Porphyromonas</i> spp.	19	0.06	0.06	0.015 - 0.125
(b) (4)				
(b) (4)				
<i>Mycobacterium abscessus</i>	20	≤0.12	0.25	≤0.06 - 1
(b) (4)				
<i>Mycobacterium chelonae</i>	26	≤0.06	0.12	≤0.06 - 0.25
(b) (4)				
<i>Mycobacterium fortuitum</i>	26	≤0.06	0.12	≤0.06 - 0.25
(b) (4)				

Tigecycline activity against glycopeptide-intermediate (GISA) and vancomycin-resistant Staphylococcus aureus

Tigecycline has been tested against 19 GISA isolates obtained from the Network on Antibiotic Resistance in *S. aureus*. The Tigecycline MIC range against these 19 isolates was 0.06 – 1 µg/mL. The GISA phenotype that limits the activity of vancomycin and teicoplanin had no effect on the MICs of tigecycline.

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Tigecycline activity against Enterococcus faecalis and Enterococcus faecium with different genetic elements conveying resistance to vancomycin

Tigecycline activity against *E. faecalis* and *E. faecium* with different genetic elements (*VanA*, *VanB* and *VanA*, *VanB* and *VanD* respectively) conveying resistance to vancomycin did not change the tigecycline MIC against these organisms compared to those *E. faecalis* and *E. faecium* isolates without the genetic elements.

Tigecycline activity against erythromycin-resistant Streptococcus pyogenes and Streptococcus agalactiae

Table 5 shows the activity of tigecycline against *S. pyogenes* and *S. agalactiae* that have the erythromycin resistance genes *mef(A)*, *erm(A)*, and *erm(B)*. Tigecycline was active against all isolates regardless of the genetic determinant responsible for the erythromycin-resistance. Of the 107 erythromycin-resistant *S. pyogenes*, 13 isolates were determined to possess the ribosomal protection determinant *tet(M)*. Among the 98 isolates of erythromycin-resistant *S. agalactiae*, 66 isolates possessed *tet(M)*, and 19 isolates possessed *tet(O)*, an other gene conferring tetracycline-resistance via ribosomal protection. Tigecycline was active against all isolates regardless of the genetic elements present that were related to either erythromycin or tetracycline resistance or the combination of erythromycin and tetracycline resistance.

Table 5

Organism	Ery R phenotype	[N]	Genetic determinant			Tigecycline MIC (µg/mL) ^a		
			<i>mef(A)</i>	<i>erm(B)</i>	<i>erm(A)</i>	Range	MIC ₅₀	MIC ₉₀
<i>S. pyogenes</i>	All	107	89	9	19	0.016-0.06	0.03	0.06
	M ^b	88	88		9			
	iMLS _B	9	1	1	9			
	cMLS _B	10		8	1			
<i>S. agalactiae</i>	All	98	10	64	58	0.03-0.25	0.06	0.12
	M	6	6		3			
	iMLS _B	25	4	16	18			
	cMLS _B	67		48	37			

^a MICs determined by non-reference agar dilution tests.

^b M-M phenotype, efflux mediated resistance to macrolides only; iMLS_B- inducible macrolide-lincosamide-streptogramin B resistance (iMLS_B); cMLS_B- inducible macrolide-lincosamide-streptogramin B resistance (cMLS_B)

Tigecycline activity against gram-positive bacteria with decreased susceptibility or resistance to linezolid

Table 6 shows the activity of tigecycline against MRSA and MSSA as well as vancomycin-susceptible and –resistant *E. faecium* that had decreased susceptibility or were resistant to linezolid. As can be seen the Tigecycline MIC_{90s} for these organisms was ≤0.5 µg/mL.

Table 6

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Table 1.4.1.1.6-1: Activity of tigecycline against linezolid-resistant *S. aureus* and *E. faecium*.²¹

Organism [N]	Antibiotic	MIC (µg/mL) ^a		
		Range	MIC ₅₀	MIC ₉₀
<i>S. aureus</i> , MRSA [249]	Tigecycline	0.12-2	0.25	0.5
	Linezolid	0.5->32	2	4
<i>S. aureus</i> , MSSA [250]	Tigecycline	0.12-1	0.25	0.25
	Linezolid	1->32	2	4
<i>E. faecium</i> , VSE [204]	Tigecycline	0.12-1	0.25	0.5
	Linezolid	0.25->64	8	64
<i>E. faecium</i> , VRE [71]	Tigecycline	0.12-0.5	0.25	0.25
	Linezolid	1->32	2	2

^a MICs determined by non-reference broth-dilution tests

In summary, no significant differences were noted between the MICs of tigecycline for linezolid-susceptible and -resistant *S. aureus* and *E. faecium* in any of the studies.

Tigecycline activity against Enterococcus spp. resistant to quinupristin-dalfopristin

The Applicant in this submission (Section 2.7.2.4 Table 1.4.1.1.7-1) provides data that shows that isolates of *E. faecalis* and *E. faecium* that have been found to be resistant to quinupristin-dalfopristin to date maintain their susceptibility to tigecycline (MIC₉₀ ≤0.25 µg/mL).

Tigecycline activity against bacteria harboring classical tetracycline resistance determinants

The applicant has provided data (Section 2.7.2.4 Table 1.4.1.1.8-1) on the activity of tigecycline against bacteria harboring classical mechanisms of resistance to tetracyclines. This information can be seen in Table 6. As can be seen tigecycline maintains its activity against bacteria that harbor classical mechanisms of resistance to tetracyclines.

Table 6

Table 1.4.1.1.8-1: In Vitro Activity Of Tigecycline, Minocycline, and Tetracycline Against Strains With Characterized Tetracycline-Resistance Determinants⁵

Organism	Tet Determinant	Phenotype	MIC (µg/mL) ^a		
			Tigecycline	Minocycline	Tetracycline
<i>E. coli</i>	<i>tet(A)</i>	Efflux	0.5	4	32
<i>E. coli</i>	<i>tet(B)</i>	Efflux	0.5	16	>32
<i>E. coli</i>	<i>tet(C)</i>	Efflux	0.25	4	>32
<i>E. coli</i>	<i>tet(D)</i>	Efflux	0.25	8	>32
<i>E. coli</i>	<i>tet(M)</i>	Ribosomal Protection	0.25	>32	>32
<i>E. coli</i>	none	Susceptible	0.25	1	1
<i>S. aureus</i>	<i>tet(K)</i>	Efflux	0.5	0.25	>32
<i>S. aureus</i>	<i>tet(M)</i>	Ribosomal Protection	0.5	4	>32
<i>S. aureus</i>	none	Susceptible	0.25	0.06	0.12
<i>E. faecalis</i>	<i>tet(M)</i>	Ribosomal Protection	0.25	16	>32
<i>E. faecalis</i>	none	Susceptible	0.25	1	8

^a MICs determined by non-reference method (agar dilution)

Tigecycline activity against extended-spectrum β-lactamase (ESBL) producing strains of Enterobacteriaceae

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The applicant has provided data on the activity of tigecycline against Enterobacteriaceae that produce ESBLs (Section 2.7.2.4 Table 1.4.1.1.7.10-1 and 10-2) The data in Table 7 represent isolates collected from blood stream infections in patients from North America and, Latin America, and Europe. The data in table 8 represent isolates from patients in Europe and the Middle East. In both tables it can be seen that there was no significant differences between MICs for ESBL positive isolates compared to ESBL negative isolates.

Table 7

Table 1.4.1.1.10-1: The activity of tigecycline tested against 176 <i>E. coli</i> and <i>K. pneumoniae</i> isolates, including 96 ESBL producing strains. ²²					
Organism	ESBL ^b [N]	Antimicrobial Agent	MIC ($\mu\text{g/mL}$) ^a		
			Range	MIC ₅₀	MIC ₉₀
<i>E. coli</i>	Neg [43]	Tigecycline	0.06-2	0.12	0.25
		Tetracycline	≤ 4 ->8	≤ 4	>8
		Imipenem	≤ 0.06 -1	0.12	0.25
		Piperacillin/tazobactam	0.5->128	2	8
		Ciprofloxacin	≤ 0.25 ->2	≤ 0.25	>2
	Pos [35]	Tigecycline	0.06-0.5	0.12	0.5
		Tetracycline	≤ 4 ->8	>8	>8
		Imipenem	≤ 0.06 -0.5	0.12	0.5
		Piperacillin/tazobactam	1->128	128	>128
		Ciprofloxacin	≤ 0.25 ->2	≤ 0.25	>2
<i>K. pneumoniae</i>	Neg [37]	Tigecycline	0.06-4	0.25	1
		Tetracycline	≤ 4 ->8	≤ 4	>8
		Imipenem	≤ 0.06 -0.5	0.12	0.25
		Piperacillin/tazobactam	0.12-128	4	8
		Ciprofloxacin	≤ 0.25 ->2	≤ 0.25	≤ 0.25
	Pos [61]	Tigecycline	0.06-4	0.25	1
		Tetracycline	≤ 4 ->8	≤ 4	>8
		Imipenem	≤ 0.06 -2	0.25	0.5
		Piperacillin/tazobactam	4->128	>128	>128
		Ciprofloxacin	≤ 0.25 ->2	≤ 0.25	>2

a. MICs determined by non-reference broth microdilution tests

b. ESBL phenotype determined by NCCLS recommended confirmatory test.²⁶

Table 8

Table 1.4.1.1.10-2: In vitro MIC values of tigecycline and other antibiotics against 420 ESBL producing and 516 non-ESBL producing <i>E. coli</i> and <i>K. pneumoniae</i> . ²¹					
Organism	ESBL ^b [N]	Antimicrobial Agent	MIC (µg/mL) ^c		
			Range	MIC ₅₀	MIC ₉₀
<i>E. coli</i>	Neg [258]	Tigecycline	0.12-1	0.25	0.5
		Ceftazidime	0.5->64	0.5	0.5
		Ceftriaxone	0.5->64	0.5	0.5
		Imipenem	0.5-1	0.5	0.5
	Pos [142]	Tigecycline	0.25-2	0.25	1
		Ceftazidime	0.5->64	32	>64
		Ceftriaxone	0.5->64	32	>64
		Imipenem	0.5-1	0.5	0.5
<i>K. pneumoniae</i>	Neg [258]	Tigecycline	0.12-8	0.5	1
		Ceftazidime	0.5->64	0.5	1
		Ceftriaxone	0.5->64	0.5	0.5
		Imipenem	0.5-1	0.5	0.5
	Pos [278]	Tigecycline	0.25-8	1	2
		Ceftazidime	0.5->64	>64	>64
		Ceftriaxone	0.5->64	16	>64
		Imipenem	0.5-4	0.5	0.5

c. MICs determined by non-reference broth microdilution tests

d. ESBL phenotype determined by NCCLS recommended confirmatory test.²⁶

Tigecycline activity against ciprofloxacin-resistant Escherichia coli

The Applicant has provided data for *E. coli* to show that tigecycline activity is not influenced by the susceptibility of *E. coli* to ciprofloxacin (Section 2.7.2.4 Table 1.4.1.1.7.11-1). The tigecycline MIC₉₀ for both ciprofloxacin-susceptible and –resistant *E. coli* is 1µg/mL.

Activity of tigecycline against intracellular pathogens

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The Applicant indicates (Section 2.7.2.4 subsection 1.6.4.3.2) tigecycline is active against the intracellular pathogens *Chlamydia pneumoniae* and *Chlamydia trachomatis*. This information suggests that tigecycline penetrates into human cells since these studies were done in cultured cells.

Mechanism of Action

Tetracyclines act by inhibiting protein translation in bacteria, presumably by binding to the 30S ribosomal subunit and blocking entry of amino-acyl transfer RNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into the elongating peptide chains. In general, tetracyclines are considered bacteriostatic. Glycylcyclines inhibit protein synthesis on wild-type ribosomes and on *tetM*-protected, tetracycline-resistant ribosomes and they also inhibit organisms with tetracycline efflux mechanisms (1,7). Tigecycline has been shown to overcome the major tetracycline resistance mechanisms of efflux and ribosomal protection and to have in vitro activity against multidrug-resistant staphylococci (see Table 1), penicillin-resistant *S. pneumoniae* (see Table 1), vancomycin-resistant enterococci (see Table 1), anaerobes (see Table 1), and minocycline-resistant bacteria while retaining activity against minocycline-susceptible microorganisms (3,8).

Current evidence suggests that tigecycline binds more avidly to the ribosomes such that the product of the *tet(M)* gene is unable to disrupt the tight glycylcycline-ribosome bond or that the product of the *tet(M)* gene is unable to interact with the ribosome to allow protein synthesis to occur (9,10). The activity of tigecycline against isolates of bacteria that have efflux mechanisms of resistance likely results either from the inability of tigecycline to induce tetracycline efflux proteins or simply because the efflux pump is ineffective in transporting glycylcyclines out of the cell.

Table 9 shows the MICs of tigecycline, tetracycline, and minocycline against some gram-positive and gram-negative bacteria with known tetracycline resistance determinants.

Table 9. In vitro MICs of tigecycline, minocycline and tetracycline against gram-positive and gram-negative bacteria with known tetracycline resistance determinants (6)

Organism	Resistance Determinant	MIC (µg/mL)		
		Tigecycline	Minocycline	Tetracycline
<i>Escherichia coli</i>	<i>tet(B)</i>	0.5	16	>32
<i>E. coli</i>	<i>tet(A)</i>	2	4	32
<i>E. coli</i>	<i>tetC</i>	2	4	>32
<i>E. coli</i>	<i>tet(D)</i>	0.25	8	>32
<i>E. coli</i>	<i>tet(M)</i>	0.25	>32	>32
<i>Staphylococcus aureus</i>	<i>tet(K)</i>	0.5	0.25	0.32
<i>S. aureus</i>	<i>tet(M)</i>	0.5	4	0.32

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<i>E. faecalis</i>	<i>tet(M)</i>	0.25	16	>32
<i>Neisseria gonorrhoeae</i>	<i>tet(M)</i>	1	16	>32

In this submission (Section 2.7.2.4, subsection 1.5.2.1) the Applicant provides the following information on the bactericidal/bacteriostatic activity of tigecycline against a variety of bacteria. As noted tigecycline is bactericidal against *S. pneumoniae*, regardless of susceptibility to penicillin but bacteriostatic against the majority of *S. aureus*, *E. coli*, and *K. pneumoniae*.

1.5.2.1 MIC/MBC ratios⁷⁻¹¹

The minimal bactericidal concentration (MBC) of tigecycline was determined by several investigators against recent clinical isolates using methods recommended by the National Committee for Clinical Laboratory Standards (NCCLS) (5.3.5.4: RPT-42704, RPT-51233, RPT-51962, RPT-51227).^{7-9, 11, 12} Minimal inhibitory concentrations (MICs) were determined by

microbroth dilution methods as recommended by the NCCLS.¹³ Samples from culture wells showing inhibition of growth by the unaided eye after 24 hr of growth at 35°C-36°C were sub-cultured onto antibiotic-free growth medium plates with the appropriate supplements where required. The plates were incubated for 18-24 hr at 35°C after which colony counts were determined. The MBC was defined as the lowest concentration of antibiotic that results in a 3- \log_{10} (99.9%) decrease in CFU/mL of the inoculum. If the MBC is within 4 dilutions of the MIC, the antibiotic activity is considered to be bactericidal.

On the basis of MIC/MBC ratios tigecycline was bactericidal against 62 of 64 *Streptococcus pneumoniae* isolates (5.3.5.4: RPT-42704, RPT-51233, RPT-51962).⁷⁻⁹ The two exceptions were a penicillin-susceptible strain and the ATCC reference strain (5.3.5.4: RPT-42704).⁷ Bactericidal activity was noted against penicillin-susceptible (PSSP), penicillin-intermediate and penicillin-resistant *S. pneumoniae* (PRSP) isolates (5.3.5.4: RPT-42704, RPT-51233).⁷⁻⁸ The MBC₉₀/MIC₉₀ ratio was ≥ 2 against 14 methicillin-susceptible *S. aureus* (MSSA) and 17 methicillin-resistant *S. aureus* (MRSA) indicating bactericidal activity against these isolates (5.3.5.4: RPT-51962).⁹ Tigecycline was not bactericidal against 26 MRSA isolates (5.3.5.4: Patel R, 2000)¹⁰ or the 3 MSSA, 3 MRSA, and 2 of the 6 MS- and MR-coagulase-negative staphylococci isolates tested (5.3.5.4: RPT-42704).⁷ Stevens determined the MIC and MBC for ten strains of *Streptococcus pyogenes* (5.3.5.4: RPT-51227).¹¹ Tigecycline MICs ranged from 0.03-0.06 $\mu\text{g/mL}$, whereas MBCs ranged from 0.06-0.24 $\mu\text{g/mL}$. For most of the strains, the MBC was 1 to 3 dilutions higher than the MIC. Bacteriostatic activity was observed against *Enterococcus faecalis* or *E. faecium* including both vancomycin-susceptible and vancomycin-resistant strains. Bacteriostatic activity was also noted against many of the 20 *E. coli* and 20 *K. pneumoniae* clinical isolates tested (5.3.5.4: RPT-51962).⁹ Thus tigecycline demonstrates bactericidal activity against most penicillin-susceptible, -intermediate and -resistant *S. pneumoniae* and occasional isolates of *S. aureus*, *E. coli* and *K. pneumoniae*.

Mechanism(s) of Resistance

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Mutations in the interdomain loop region of the *tet(A)* tetracycline resistance gene that increase the efflux of minocycline and glycylicyclines has been reported in veterinary isolates of *Salmonella choleraesuis* and *Salmonella typhimurium* isolates (11). These mutations were shown to reduce susceptibility to the glycylicycline class of antibiotics. This reduced susceptibility was more pronounced for the glycylicyclines DMG-MINO and DMG-DMOT than GAR-936 (TBG-MINO) (8 to 16 µg/mL vs. 2 µg/mL respectively) (12). The authors of this report noted that both isolates carried the same novel *tet(A)* variant, based on DNA sequencing, with one determinant plasmid encoded and the other on the chromosome. The novel *tet(A)* gene carries two mutations in the largest cytoplasmic loop of the efflux pump, which causes a double frameshift in codons 201, 202 and 203. This “interdomain region” of the efflux pump the authors note has generally been regarded as having no functional role in the efflux of tetracycline but the double frameshift is most likely responsible for the enhanced resistance observed and points to an interaction that was previously unrecognized. The authors also note that mutants of the *tet(B)* class with decreased susceptibility to the glycylicyclines were also generated in vitro. These all carried mutations in the portion of the *tet(B)* gene encoding a transmembrane spanning region of the efflux pump. The authors suggest that it will be the interdomain region of the pump that is likely to be the loci of future glycylicycline resistance mutations as these compounds enter clinical use (11). How, commonly this resistance will occur as the glycylicyclines are used is unclear at this time.

Genera with intrinsic decreased susceptibility to Tigecycline

Proteae (*Proteus* spp., *Providencia* spp. and *Morganella* spp.) and *Pseudomonas aeruginosa* are inherently less susceptible to tigecycline than most other bacteria. The Applicant provides information on the mechanism(s) that contribute to the resistance of these bacteria to tigecycline (Section 2.7.2.4, subsection 1.4.2.1). In the case of *Proteus mirabilis* it was found that two independent transposon insertion mutants are responsible for the decreased susceptibility of this organism to tigecycline. It was determined that the transposon had inserted the *acrB* gene, which is part of the AcrAB efflux system and belongs to the resistance, modulation and cell division (RND) family. This efflux system pumps out a broad range of antibiotics, detergents and dyes. It is well characterized in other genera of the family *Enterobacteriaceae*, but had not been previously identified in *P. mirabilis*. Although *E. coli*, *K. pneumoniae* and *E. aerogenes* have close homologs to the AcrAB efflux system, wild-type strains do not show decreased susceptibility to tigecycline.

In the case of *Morganella morganii* (Section 2.7.2.4, subsection 1.4.2.2) the Applicant has determined that the presence of the transposon that regulates the Acr pump is the likely cause for reduced susceptibility of *M. morganii* to tigecycline.

For *P. aeruginosa* an efflux pump is also related to the decreased tigecycline susceptibility. The specific efflux pump in *P. aeruginosa* has been found to be MexXT-oprM (Section 2.7.2.4, subsection 1.4.2.3).

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Synergism/Antagonism Studies (Antibacterial Interactions and Fixed Combination Studies)

The Applicant has provided information on the activity of tigecycline in combination with other antimicrobials against a variety of bacteria (Section 2.7.2.4 subsection 1.7). For the in vitro antibacterial studies the Applicant has used the following definitions of synergism and antagonism. Synergism was defined as a \geq two-fold dilution increase in the combination MIC when compared to the MICs of either agent while antagonism was defined as a \geq two-fold dilution increase in the combination MIC when compared to the MICs of either agent alone. A single dilution increase or decrease was considered to be non-significant and referred to as “indifferent” result.

The antibacterial activity of tigecycline was determined in a 1:1 combination with gentamicin, ciprofloxacin, vancomycin, erythromycin, piperacillin, imipenem, and rifampin, amikacin, ampicillin-sulbactam, azithromycin, ciprofloxacin, colistin, levofloxacin, minocycline, piperacillin, piperacillin-tazobactam, and polymyxin B. Synergistic activity was shown for *E. faecalis* PT4440 and *S. pneumoniae* GC1889 with a tigecycline plus erythromycin combination. The respective tigecycline and erythromycin MICs for *E. faecalis* PT4440 were 0.12 μ g/mL and 1 μ g/mL, whereas the combination showed an activity of 0.015 μ g/mL (i.e. 0.015 μ g/mL of each agent). Similarly, the combination MIC for the *S. pneumoniae* GC1889 isolate was 3 and 6 dilutions lower than the tigecycline and erythromycin MICs alone respectively. However, the Applicant concluded from all the synergy/antagonism studies that were conducted that there were no consistent trends for synergy and no antagonism between tigecycline and any antibiotic in combination for any of the bacterial species tested.

IN VITRO SUSCEPTIBILITY TEST METHODS

Broth dilution susceptibility tests for tigecycline require the use of fresh media

Susceptibility testing with tigecycline in broth requires the use of fresh media that is less than 12 hours old at the time that the drug is diluted in the broth media. The reason for this is that tigecycline is susceptible to oxidative degradation. MIC tests for aerobic organisms in fresh media are referred to by the Applicant as the “reference method” for tigecycline. This methodology has been approved for use by the Clinical Laboratory and Standards Institute (formerly known as the National Committee for Clinical Laboratory Standards) (5,6). The Applicant in this submission has provided in subsection 1.6.1 of section 2.7.2.4 (Special Studies) of this submission the rationale and data to support this requirement for in vitro susceptibility testing in broth media. The key to this caveat is the need to add the drug to broth media that is <12 hours old. If the drug is added to broth media <12 hours old and the broth media with the drug is immediately frozen and the plates used for susceptibility testing with 12 hours of use there is no effect on the MIC of aerobic bacteria. The Applicant in subsection 1.6.1 of section 2.7.2.4 (Special Studies) of this submission has provided experimental data to support this fact. Only the testing of

facultative bacteria is effected since anaerobic testing is done under anaerobic conditions and thus there is no oxygen to oxidatively degrade the tigecycline.

Effect of pH on the activity of tigecycline

The Applicant in this submission (Section 2.7.2.4 subsection 1.6.1.2) provides data to show that there was only a slight increase, one log₂ dilution for most bacteria tested, when the pH decreased from pH 7 to pH 5 (Table 1.6.1.2.1). Similarly no significant difference in the MICs of tigecycline was observed when the medium pH was raised from 7.0 to 9.0.

Effect of inoculum density on the activity of tigecycline

The Applicant in this submission (Section 2.7.2.4 subsection 1.6.1.2.2) provides information on the effect of inoculum density on the MIC of tigecycline. Basically the information shows that for both gram-positive and gram-negative clinical isolates the tigecycline MIC was not significantly affected (defined as ≥ 2 fold dilution change) by increasing the inoculum density above the standard to 10⁶ and 10⁷ CFU/mL or below 10⁴ CFU/mL.

Comparison of tigecycline MICs determined by agar dilution and MICs determined by broth microdilution

The Applicant has provided information (Section 2.7.2.4 subsection 1.6.1.3) to show that overall tigecycline MICs generated by agar dilution tended to be 1-log₂ dilution higher than those determined by broth microdilution.

Development of disk test for diffusion tests with tigecycline

The Applicant carried out studies (Section 2.7.2.4 subsection 1.6.2) to select the disk content of tigecycline that most accurately differentiates between susceptible and resistant organisms. Disks containing 5, 10, 15 and 30 µg of tigecycline were tested. Zones of inhibition in mm using the Kirby-Bauer disk diffusion test were compared with the minimum inhibitory concentration (MIC) using the standard microbroth 2-fold serial dilution method as recommended by NCCLS (4, 13). A variety of bacteria (see Table 10) were included in the testing. Results for each of the disk contents and the corresponding MICs for the test organisms were analyzed by the error-rate bounded analysis. Initial analysis indicated that both the 15 and 30 µg disks gave good separation between susceptible and resistant isolates. Further analysis showed that the 15 µg disk provided the best dose-response and separation of susceptible and resistant isolates (Section 2.7.2.4 subsection 1.6.2.1). Stability studies showed that the disk content remained within the acceptable range by CFR guidelines after 3.5 years at 4°C (Section 2.7.2.4 subsection 1.6.2.2).

Table 10.

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Table 1.6.2.1-1: Bacterial Strains used in development of tigecycline disk for Kirby-Bauer susceptibility tests²¹

ORGANISM	No. OF STRAINS	MIC RANGE (µg/ml)	
		Tigecycline	Minocycline
<i>E. coli</i>	35	0.125 - 1	0.25 - 64
<i>K. pneumoniae</i>	11	0.25 - 0.5	1 - 4
<i>K. oxytoca</i>	11	0.125 - 0.5	1 - 8
<i>C. diversus</i>	10	0.125 - 0.5	0.5 - 4
<i>C. freundii</i>	10	0.25 - 4	2 - 16
<i>E. cloacae</i>	10	0.25 - 1	2 - 8
<i>E. aerogenes</i>	10	0.25 - 2	2 - 8
<i>H. alvei</i>	8	0.25 - 1	1 - 8
<i>P. mirabilis</i>	15	1 - 4	8 - 64
<i>P. vulgaris</i>	13	1 - 4	4 - 32
<i>Providencia</i> sp.	9	0.5 - 8	2 - >64
<i>P. rettgeri</i>	5	0.25 - 16	2 - >128
<i>M. morgani</i>	11	0.5 - 8	1 - >128
<i>Salmonella</i> sp.	22	0.25 - 2	0.5 - >64
<i>Shigella</i> sp.	20	0.03 - 0.125	0.5 - 8
<i>S. marcescens</i>	20	0.5 - 1	0.06 - 0.25
<i>Y. enterocolitica</i>	5	0.125 - 0.25	0.5 - 1
<i>P. aeruginosa</i>	18	4 - 32	8 - 128
<i>S. maltophilia</i>	10	0.5 - 2	2 - 16

Table 1.6.2.1-1: Bacterial Strains used in development of tigecycline disk for Kirby-Bauer susceptibility tests²¹ (Cont'd)

ORGANISM	No. OF STRAINS	MIC RANGE (µg/ml)	
		Tigecycline	Minocycline
<i>Acinetobacter</i> sp.	20	≤0.06 - 8	≤0.06 - 8
<i>B. cepacia</i>	10	0.25 - 2	0.06 - 1
<i>S. aureus</i> (MSSA)	20	0.125 - 1	0.06 - 8
<i>S. aureus</i> (MRSA)	24	0.125 - 0.5	≤0.03 - 8
<i>S. haemolyticus</i>	10	0.06 - 1	0.03 - 1
<i>S. epidermidis</i> (MSSE)	20	0.06 - 0.5	0.06 - 0.5
<i>S. epidermidis</i> (MRSE)	18	0.125 - 1	0.06 - 8
Other CNS sp	10	0.06 - 1	0.06 - 1
<i>S. pneumoniae</i> (PEN:R)	9	0.06 - 4	2 - 16
<i>S. pneumoniae</i> (PEN:S)	7	0.25 - 2	0.06 - 2
<i>S. agalactiae</i>	10	0.03 - 0.25	0.06 - 16
<i>S. pyogenes</i>	11	0.06 - 0.25	0.06 - 0.125
<i>E. casseliflavus</i>	2	0.125	16
<i>E. faecalis</i>	20	0.06 - 0.125	0.06 - 16
<i>E. faecium</i>	17	≤0.03 - 0.125	≤0.03 - 16
<i>E. gallinarum</i>	4	0.06 - 0.25	16
<i>E. raffinosus</i>	5	≤0.06 - 0.5	0.5 - 4
Total	470		

Quality control limits for disk susceptibility tests of 15 µg tigecycline disk

In accordance with guidelines set by NCCLS (now CLIS) document (14), a collaborative study was performed in eight different laboratories using two 15 µg disks prepared by two manufacturers, (b) (4). The data accumulated from the eight participating laboratories were pooled and the quality control zone size limits for the 15 µg disks for each of the reference organisms were determined. A review of the data submitted in this application to establish the quality control zones found no problems with the data used to establish the quality control ranges for the 15 µg tigecycline disk. These results can be seen in Table 11.

Quality Control Limits for Broth Microdilution Susceptibility Testing of Facultative Bacteria for Tigecycline

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A number of studies were conducted by the Applicant in order to establish the tigecycline broth microdilution quality control ranges for facultative bacteria. This was necessary because at the beginning of the development of tigecycline it was not realized that (b) (4) broth no older than 12 hours needed to be used because of the (b) (4) (b) (4) of tigecycline in broth media older than 12 due to the (b) (4) (b) (4). All studies used to establish the tigecycline broth microdilution quality control ranges were done in accordance with NCCLS M-23 guidelines (14). Table 11 shows the broth micro-dilution quality control ranges that were determined after the numerous studies.

Tigecycline Quality Control for Dilution Tests for Anaerobic Organisms

The Applicant in this submission provides data used to establish tigecycline broth micro-dilution quality control ranges. All procedures used to establish these quality control ranges followed the guidelines of the NCCLS (14,15). The tigecycline quality control ranges for the agar dilution method that were established are shown in Table 11. The Applicant attempted to establish tigecycline quality control ranges for anaerobic bacteria test by broth microdilution but was not able to do this. Quality control ranges for anaerobes could be established for anaerobes therefore anaerobe susceptibility testing must be done by agar dilution. Broth micro-dilution susceptibility testing of anaerobes to determine MICs is not recommended.

Table 11.

Table 1.6.3.4-1: NCCLS approved quality control ranges for tigecycline ^{2,3}		
Organism	Dilution testing MIC (µg/mL)	Disk Diffusion Zone Diameter
<i>S. aureus</i> ATCC 25923	NA ^a	20 to 25 mm
<i>S. aureus</i> ATCC 29213	0.03-0.25 µg/mL ^b	NA
<i>E. coli</i> ATCC 25922	0.03-0.25 µg/mL	20 to 27 mm
<i>E. faecalis</i> ATCC 29212	0.03-0.12 µg/mL	NA
<i>P. aeruginosa</i> ATCC 27853	No range approved	9 to 13 mm
<i>S. pneumoniae</i> ATCC 49619	0.016-0.12 µg/mL	23 to 29 mm
<i>H. influenzae</i> ATCC 49247	0.06-0.5 µg/mL	23 to 31 mm
<i>N. gonorrhoeae</i> ATCC 49226	NA	30 to 40 mm
<i>B. fragilis</i> ATCC 25285	0.12-1 µg/mL ^c	NA
<i>B. thetaiotaomicron</i> ATCC 29741	0.5-2 µg/mL	NA
<i>E. lentum</i> ATCC 43055	0.06-0.5 µg/mL	NA

^a NA, not applicable for this organism

^b For broth microdilution testing of tigecycline, when MIC panels are prepared, the medium must be prepared fresh on the day of use. The medium must be no greater than 12 hours old at the time the panels are made, however the panels may then be frozen for later use.

^c Quality control ranges for anaerobes were determined for agar dilution only

Development of provisional interpretive criteria for dilution tests for tigecycline

The Applicant in a previous submission had provided the rationale and data for the establishment of provisional tigecycline MIC interpretive criteria (IND 56,518 SN 090 dated 19 Oct 2001). The proposed breakpoints of (b) (4)

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(b) (4) were based on the following preclinical in vitro susceptibility data, pharmacological properties and clinical efficacy data from Phase II studies. The MIC interpretive criteria promoted by the Applicant at this time was not based on any bacteriological eradication or clinical out come data from clinical studies.

- For GAR-936 (previous name of tigecycline), MIC_{90s} for many types of pathogenic bacteria tested was 2 µg/mL or lower
- GAR-936 provided a long in vitro and vivo PAE for both *S. pneumoniae* and *E. coli*
- GAR 936 was well distributed to most tissues and the concentration of GAR-936 in these tissues are higher than in plasma
- Animal studies showed a significant time above an MIC of 2 µg/mL in many tissues including cardiac vegetations
- GAR penetrates into human cells as demonstrated by efficacy against intracellular pathogens
- The time above the MIC in serum did not correlate with the efficacy in animal studies in any of the infection models studied
- From these infection models, the currently used clinical daily dose of 100 mg would be efficacious for difficult to cure infections such as endocarditis
- There was a clinical cure associated with the majority of patients that had pathogens susceptible to ≤ 2 µg/mL of GAR-936 in preliminary data from Phase II clinical trials

Development of provisional interpretive criteria for disk diffusion tests for tigecycline

The Applicant also established provisional disk diffusion interpretive criteria for tigecycline based on the determined provisional MIC interpretive criteria. The zone diameter interpretive criteria were (b) (4)

When the data from all organisms used to determine the disk diffusion interpretive criteria were analyzed by the error-rate bounded method (14) there was good correlation between MIC and zone diameters (no very major or major errors resulted (Table 12). These zone diameters also fit the criteria outlined by the NCCLS in their M23 document (14) that 1) most susceptible strains should produce zone diameters between 15 and 45 mm, and 2) that the susceptible breakpoint should be between 15 and 25 mm.

Table 12 shows the correlation between the Applicant's proposed MIC interpretive criteria and the Applicant's proposed disc diffusion interpretive criteria.

Table 12

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MIC Range	Number of Isolates	Number of Discrepancies (Discrepancy Rate)		
		Very Major (%)	Major (%)	Minor (%)
$\geq(1+2)$	21	0	NA	1 (4.8)
(I+1) to (I-1)	176	4 (2.3)	0	72 (40.9)
$\leq(1-2)$	1043	NA	0	5 (0.5)
Total	1240	4 (2.3)	0	78 (6.3)

IN VIVO

Pharmacokinetics

Figure 1 represents GAR-936 (aka tigecycline) individual and mean serum concentration vs. time profiles obtained after the last dose of GAR-936 on day 10 (steady state) in healthy subjects after 50 mg bid dosing. The drug is rapidly distributed from the serum to the tissues. The mean AUC_{0-12} obtained at steady-state after 50 mg bid doses in healthy volunteers was 3.1 $\mu\text{g}\cdot\text{h}/\text{mL}$. This translates to a total serum AUC of 6.2 $\mu\text{g}\cdot\text{h}/\text{mL}$. This concentration of tigecycline in the blood after a total daily dose of 100 mg provides adequate serum concentration to treat the target pathogens (see In Vitro Spectrum of Activity).

The long half-life of GAR-936 (mean $T_{1/2} > 30$ h) seen in humans is believed by the Applicant to be due to the prolonged residence of the drug in the body. The Applicant has provided information from both animal and human studies to show that tigecycline is extensively distributed into tissues (Table 13) (Section 2.7.2.4 subsection 1.6.4.3.3). In a previous submission (study GTR33609) the Sponsor provided data on the efficacy of tigecycline to treat pneumonia caused by *S. pneumoniae* in mice. The data showed that maximum reduction of 4.7 to 5 \log_{10} against penicillin-resistant *S. pneumoniae* was at 72 hours after administration of 8 mg/kg of tigecycline. The 8 mg/kg treatment was fractionated into BID (4 mg/kg) and QID (2 mg/kg) dosing. The BID and QID results showed slightly better efficacy, however the counts were below the levels of detection and the maximum reduction $> 5 \log_{10}$ was recorded. The percent survival of mice infected with penicillin-susceptible and –resistant *S. pneumoniae* after subcutaneous administration of 1mg/kg was 100%. In these studies tigecycline was shown to achieve lung tissue concentrations above the MIC to PRSP for approximately 4 hours at 4mg/kg.

Theoretically, due to its long-half in humans, tigecycline concentrations approach steady-state levels only after 5 days (50 mg bid). Therefore, a 100 mg loading dose followed 12 hours later by 50 mg q12h was chosen by the Applicant for rapidly achieving steady-state levels in humans. The Applicant feels that because of the long half-life of tigecycline it is amenable to once daily dosing. However, nausea and vomiting is the dose limiting tolerability factor.

Figure 1

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Figure 1.6.4.3.3-1: Serum concentration vs. Time Profiles of GAR-936 in Humans After Last Dose on Day 10 (Steady-state) Following 50 mg bid Dosing as a 1 hour Infusion (study 3074A1-101-US)⁴⁵

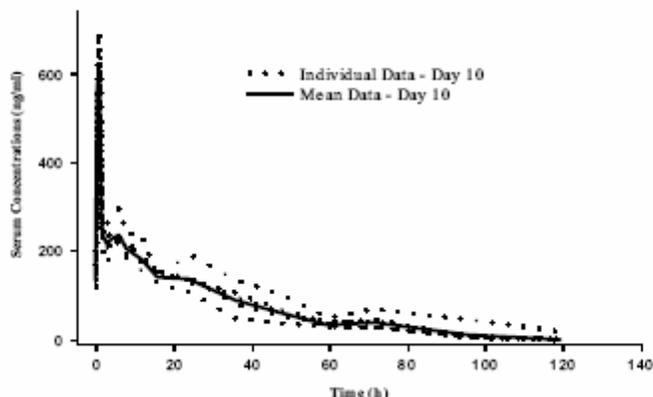


Table 13

Table 1.6.4.3.1-1: Comparison of Time Above MIC₉₀ (or a Fraction) in Tissues – Results from Simulation of Tissue Distribution Data from Rats⁴⁴

Tissue	Time Above MIC ₉₀ (over a 24 hr period after 7 days QD dosing)			
	MIC ₉₀ - 2.0	MIC ₉₀ - 1.0	MIC ₉₀ - 0.5	MIC ₉₀ - 0.25
Plasma	mmor	-2	-3	-6
Skin	-2	-8	-14	-24
Lung	-3	-8	-21	+24
Salivary Gland	-16	+24	+24	+24
Kidney	-14	+24	+24	+24
Liver	-10	-18	+24	+24
Heart	-5	-10	-16	+24
Brain	-0	-0	-0	-4

Note: Simulations of total radioactivity data from a single IV dose tissue distribution study of ¹⁴C-GAR-936 in rats.

Post Antibiotic Effect (PAE)

The Sponsor in a previous submission (study GTR 33607) provided data to show what the in vitro PAE of tigecycline was after exposure of *Escherichia coli* or *S. aureus* isolates to 8 x MIC of tigecycline for two hours. The PAE's against tet-susceptible, *tet(K)*, *tet(M)* expressing *S. aureus* were >4.5, >3.5, and >3 hours for tigecycline. For enterococci the PAE, regardless of the mechanism of resistance was found to be >3 hours. The PAE's against tet-susceptible, *tet(B)*, of *tet(M)* expressing *E. coli* were 2.9, 2.6, and 1.8 hours for tigecycline. Studies have shown when tigecycline (GAR-936) is dosed at 3mg/kg the PAE for *S. pneumoniae* is 8.9 hours and for *E. coli* 4.9 hours (12). The same PAE characteristics for tigecycline in relation to *S. pneumoniae* and *E. coli* seen in vitro were seen in the mouse model (Section 2.7.2.4, subsection 1.5.1.3)

Animal Studies

The Applicant provides data for the effectiveness of tigecycline in a number of mouse efficacy models and endocarditis models (Section 2.7.2.4 subsection 1.6.4.2.3). In

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general, the in vivo data reflect the in vitro potency of these compounds. The models were: 1) an acute lethal mouse model, in which a single dose of an antibiotic is administered either intravenously or subcutaneously to prevent death from a lethal, systemic infection; 2) a localized mouse infection model, in which mice are rendered neutropenic, bacteria are injected into the thigh muscle, and bacterial counts in the thigh are determined 24 hours after infection; 3) a mouse pneumonia model, in which a bacterial culture is introduced nasally and when untreated, is lethal; and 4) a rat or rabbit endocarditis model, in which bacterial vegetations grow in catheter-induced injuries in heart tissue and the ability of antibacterial agents to inhibit growth is determined compared to untreated controls.

The efficacy of tigecycline as determined in each of the in vivo models is shown in Table 14. The pharmacokinetic properties of tigecycline were also determined for the infected animals. The results of these studies demonstrate that the time above MIC did not correlate with the efficacy in the animal studies in any of the infection models studied. From a number of these studies, area under the concentration-versus-time curve (AUC) was the determinant of the in vivo efficacy, and the AUCs listed would therefore represent the target AUC in humans.

Table 14

Model	Organism	Efficacious Dose (mg/kg)	AUC (µg•hr/mL)	T>MIC in Serum (hr/day)	Projected human dose (mg/day)
Acute lethal (mouse) ^a	<i>E. coli</i>	1.7	1.6	0	8
	<i>S. aureus</i>	0.5-2	0.48-0.57	<1-2	2.5-10
	<i>E. faecalis</i>	1	0.96	<1	5
Pneumonia (mouse) ^b	<i>S. pneumoniae</i>	1 (100%)	0.65	<1	11
	<i>K. pneumoniae</i>	5 (7%)	2.9	0	48
Endocarditis (rat) ^c	<i>E. faecalis</i>	3.5	5.4	>8	90
	<i>S. aureus</i>	3.5	5.4	1	90

^a Efficacious dose – Effective dose 50% ED₅₀

^b Efficacious dose – Protective dose 50% (PD₅₀)

^c Efficacious dose – >2 log₁₀ reduction in CFU, BID dosing

Pharmacodynamics

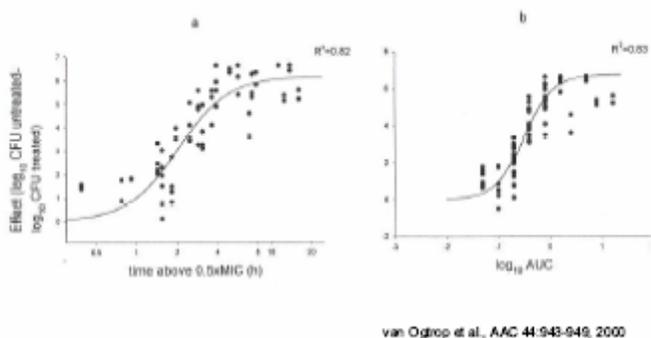
The in vivo pharmacodynamic activity of GAR 936 was assessed in an experimental murine thigh infection model in neutropenic mice (12). Mice were infected with one of several strains of *S. pneumoniae*, *S. aureus*, *E. coli*, or *K. pneumoniae*. Most infections were treated with a twice-daily dosing schedule, with the administration of 0.75 to 192 mg of GAR-936. A maximum-effect dose-response model was used to calculate the dose that produced a net bacteriostatic effect over 24 hours of therapy. More extensive dosing studies were done with *S. pneumoniae*, *E. coli*, and *K. pneumoniae*, with doses being given as one, four or eight equal doses over a period of 24 hours. The dosing schedules were designed in order to minimize the interrelationship between the various

pharmacokinetic and pharmacodynamic parameters studied. These parameters were time above 0.03 to 32 times the MIC, area under the concentration-time curve (AUC), and maximum concentration of drug in serum (C_{max}). The bacteriostatic dose remained essentially the same, irrespective of the dosing frequency for *S. pneumoniae* (0.3 to 0.9 mg/kg/day). For *E. coli* and *K. pneumoniae*, however, more frequent dosing led to lower bacteriostatic doses. Time above a certain factor (range 0.5 to 4 times) of the MIC was a better predictor of in vivo efficacy than C_{max} or AUC for most organism-drug combinations. The results suggest that in order to achieve 80% maximum efficacy, the concentration of unbound drug in the serum should be maintained above the MIC for at least 50% of the time for GAR-936 (12). These experiments showed that GAR-936 was most effective against *S. pneumoniae*, both tetracycline-susceptible and tetracycline-resistant strains with bacteriostatic doses ranging from 0.8 to 5.9 mg/kg/day. Bacteriostatic doses for *E. coli* and *S. aureus* were up to 25-fold higher. GAR-936 was only marginally effective against *K. pneumoniae* with bacteriostatic doses ranging from 65 to 151 mg/kg/day.

The Applicant provided data from a localized mouse infection (thigh) model that shows that the time above some fraction of the MIC (i.e. 1.2) or the AUC correlates best with efficacy of tigecycline. This information is shown graphically in Figure 2.

Figure 2

Figure 1.6.4.3.4-1: Time above a fraction of the MIC of GAR-936 or AUC correlates with in vivo efficacy³⁸



CLINICAL TRIALS

Correlation of Provisional Interpretive Criteria with Bacteriological Clinical Outcome

Susceptibility Tests and quality Control Data from Clinical Trials

The Applicant used a contract laboratory (b) (4) to perform all identifications and susceptibility testing of isolates obtained from patients in phase 3 clinical trials.

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Verification of Procedures Used for Testing of Patient Isolates

The Applicant in this submission provided details of the methods used by (b) (4) to have organisms shipped to their laboratories, identify isolates and test isolates for their susceptibility to tigecycline and other antimicrobials (Section 2.7.2.4 subsection 4.1 – 4.1.1). Identification of bacterial isolates was done by recognized methods (16). Susceptibility testing of patient isolates was done by the methods recommended by Clinical and Laboratory Standards Institute [formerly National Committee for Clinical Laboratory Standards (NCCLS)] (4,13,14,15). The Applicant has included in this submission the in vitro susceptibility test quality control data that was generated at the time susceptibility testing of patient isolates was done. A review of this data did not reveal any major discrepancies.

Establishment of In Vitro Susceptibility Testing Interpretive Criteria

Establishment of Tigecycline MIC Interpretive Criteria

The Applicant in this submission is proposing the MIC interpretive criteria seen in Table 15. The Applicant is basing these MIC interpretive criteria based on the susceptibility of preclinical and clinical pathogens to tigecycline, and 2) analysis of microbiological and clinical response in the microbiologically evaluable (ME) population from complicated skin and skin structure infection (cSSSI) protocols 300 and 305 and complicated intraabdominal infection (cIAI) protocols 301 and 306 based on tigecycline susceptibility. This Reviewer will analyze this data and incorporate the pharmacokinetic/pharmacodynamic parameters of tigecycline, preclinical and clinical isolates susceptibility to tigecycline, and the clinical trial experience treating infections due to target pathogens in determining if the MIC interpretive breakpoints proposed by the Applicant are appropriate.

Table 15

Table 4.2.1-1: Proposed Interpretive Criteria For Tigecycline						
Grouping	MIC (µg/mL)			Zone (mm)		
	S	I	R	S	I	R
(b) (4)						(b) (4)
<i>Streptococcus</i> spp. not <i>S. pneumoniae</i>	≤0.5	-	-	≥19	-	-
(b) (4)			(b) (4)	≥19	(b) (4)	(b) (4)
Enterobacteriaceae	≤2	4	≥8	≥19	15-18	≤14
Anaerobes	≤4	(b) (4)	(b) (4)	NA	NA	NA

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Date review completed: 15 Jun 05

STAPHYLOCOCCI

In Vitro Activity of Tigecycline against Preclinical and Clinical Isolates of Staphylococcus aureus

The analysis of staphylococci provided by the Applicant is based on *S. aureus*, as this is the only species of staphylococci for which a clinical indication for tigecycline is requested. The Applicant is requesting a tigecycline susceptible breakpoint of (b) (4) an intermediate breakpoint of (b) (4), and a resistant breakpoint of (b) (4). During the preclinical testing and testing of *S. aureus* isolates from patients enrolled in clinical studies no *S. aureus* with a tigecycline MIC of greater than 2µg/mL was detected. Because the Applicant only has data for *S. aureus* and is not seeking any other species of staphylococci the MIC interpretive criteria will be listed in the package insert as *Staphylococcus aureus*.

Table 16 presents the cumulative frequency of tigecycline susceptibility of *S. aureus* isolates from preclinical and clinical tests. As can be seen the populations of *S. aureus* tested in preclinical studies and clinical studies were similar in their susceptibility to tigecycline. The data includes both methicillin-susceptible and methicillin-resistant *S. aureus*. As seen in the preclinical susceptibility data for tigecycline against *S. aureus* the organism’s susceptibility to methicillin did not dictate the organism’s susceptibility to tigecycline. The overall percentage of isolates with a tigecycline MIC greater than 1 µg/mL is 0.4%. Figures 3 – 5 show the tigecycline MICs for preclinical and clinical MSSA and MRSA. Again it can be seen the methicillin susceptibility of *S. aureus* is independent of the tigecycline MIC with both MSSA and MRSA being inhibited by ≤2 µg/mL of tigecycline.

Table 16

Table 4.2.1.1-1: Cumulative frequency of Tigecycline Susceptibility of <i>S. aureus</i> Isolates From Preclinical and Clinical Tests.							
Cumulative % of susceptible isolates at MIC [N]	MIC (µg/mL)						
	0.03	0.06	0.12	0.25	0.5	1	2
Preclinical [325]	0.9	10.8	76.9	97.5	99.4	99.7	100.0
Clinical [1015]		1.0	73.7	98.5	99.7	100.0	
Total [1340]	0.2	3.4	74.5	98.3	99.6	99.9	100.0

Figure 3

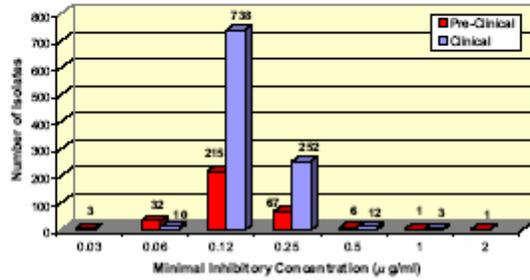
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Figure 4.3.3-4: Preclinical and Clinical Frequency Distribution of Tigecycline Minimal Inhibitory Concentrations ($\mu\text{g/ml}$) Against *Staphylococcus aureus* Group (MSSA+MRSA) (N= 325,1015)



Figures 4 - 5

Figure 4.3.3-5: Preclinical and Clinical Frequency Distribution of Tigecycline Minimal Inhibitory Concentrations ($\mu\text{g/ml}$) Against *Staphylococcus aureus* (MSSA) (N= 160,751)

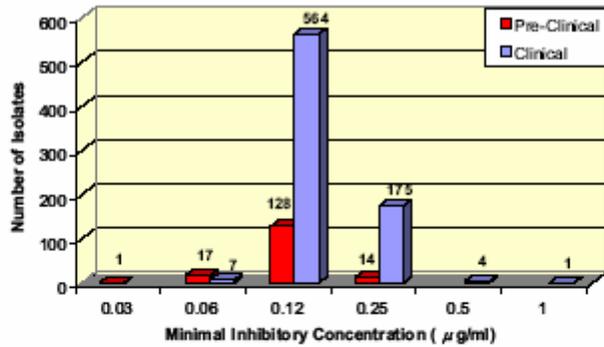
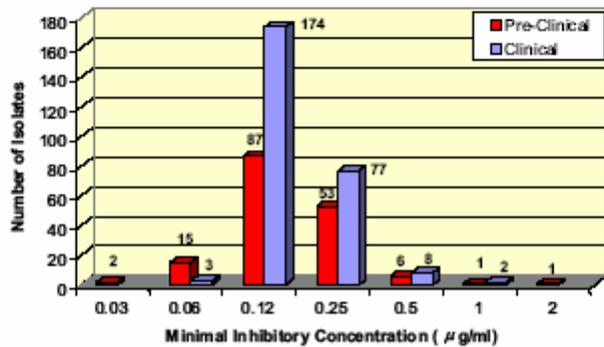


Figure 4.3.3-6: Preclinical and Clinical Frequency Distribution of Tigecycline Minimal Inhibitory Concentrations ($\mu\text{g/ml}$) Against *Staphylococcus aureus* (MRSA) (N= 165,264)



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Table 17 presents the microbiologic response from the microbiologically evaluable (ME) population from cSSSI studies for patients with *S. aureus* (includes methicillin-susceptible and –resistant isolates). As can be seen there was 87% eradication rate for all *S. aureus* isolates. For isolates with a tigecycline MIC of ≤ 0.5 $\mu\text{g/mL}$ there was an 87% (143/165) eradication rate. Tables 18 and 19 show the microbiological eradication rates individually for methicillin-susceptible and – resistant *S. aureus* obtained during the cSSSI clinical trials. Table 18, which shows the eradication rates for methicillin-susceptible *S. aureus* (all infections), shows that for MSSA with a tigecycline MIC of ≤ 0.5 $\mu\text{g/mL}$ there was an eradication rate of 89% (118/133). Table 19, which shows the eradication rates for methicillin-resistant *S. aureus* (all infections), shows that for MRSA with a tigecycline MIC of ≤ 0.25 $\mu\text{g/mL}$ there was an eradication rate of 78% (25/32). The eradication rate for the MSSA with a tigecycline MIC of ≤ 0.5 $\mu\text{g/mL}$ was somewhat better than for the MRSA. The overall distribution of eradications is similar across the MIC range for the combined, monomicrobial and polymicrobial ME populations for both MSSA and MRSA isolates. The data indicate that the rate of microbiologic eradication is uniformly distributed throughout the MIC range of 0.06 to 1 $\mu\text{g/mL}$. There is no evidence of an MIC that correlates with microbiologic persistence.

Table 17

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Table 4.2.1.1-2: Microbiological Response and MIC Distribution for the ME Population from the Integrated cSSSI Trials for *S. aureus* Isolates

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative % of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% o isolates associated with microbiological persistence at each MIC
ME-all infections					
0.06	2/2	1.2	1.4	100	0
0.12	110/128 ^a	78.3	77.8	85.9	14.1
0.25	30/34	98.8	98.6	88.2	11.8
0.5	1/1	99.4	99.3	100	0
1	1/1	100.0	100	100	0
Total	144/166			86.7	13.3
ME-monomicrobial					
0.06	0	0	0	0	0
0.12	74/88	80.7	79.6	84.1	15.9
0.25	18/20	99.1	98.9	90.0	10.0
0.5	1/1	100	100	100	0
Total	93/109			85.3	14.7
ME-polymicrobial					
0.06	2/2	3.5	3.9	100	0
0.12	36/40	73.7	74.5	100	10.0
0.25	12/14	98.2	98.0	90.0	14.3
0.5	0	98.2	98.0	0	0
1	1/1	100	100	100	0
Total	51/57			89.5	10.5

^a The clinical response at 0.12 µg/mL was 113/128. For all other MICs the clinical response was the same as the microbiological response.

Table 18

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Table 3.2-1: Microbiological Response and MIC Distribution for the ME Population from the Integrated cSSSI Trials for *S. aureus* Isolates- MSSA

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative % of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.06	1/1	0.7	0.8	100	0
0.12	91/104 ^a	78.4	77.3	87.5	12.5
0.25	25/27	98.5	98.3	92.6	7.4
0.5	1/1	99.2	99.2	100	0
1	1/1	100.0	100	100	0
Total	119/134			88.8	11.2
ME-monomicrobic					
0.12	60/69	81.2	78.9	87.0	13.0
0.25	15/15	98.8	98.6	100	0
0.5	1/1	100	100	100	0
Total	76/85			89.4	10.6
ME-polymicrobic					
0.06	1/1	2.0	2.3	100	0
0.12	31/35	73.5	74.4	88.6	11.4
0.25	10/12	98.0	97.7	83.3	16.7
0.5	0	98.0	97.7	0	0
1	1/1	100	100	100	0
Total	43/49			87.8	12.2

^a The clinical response at 0.12 µg/mL was 94/104. For all other MICs the clinical response was the same as the microbiological response.

Table 19

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Table 3.2-2: Microbiological Response and MIC Distribution for the ME Population from the Integrated cSSSI Trials for *S. aureus* Isolates- MRSA

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative % of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.06	1/1	3.1	4	100	0
0.12	19/24	78.1	80	79.2	20.8
0.25	5/7	100	100	71.4	28.6
Total	25/32			78.1	21.9
ME-monomicrobial					
0.12	14/19	79.2	82.3	73.7	26.3
0.25	3/5	100	100	60.0	40
Total	17/24			70.8	29.2
ME-polymicrobial					
0.06	1/1	12.5	12.5	100	0
0.12	5/5	75.0	75.0	100	0
0.25	2/2	100	100	100	0
Total	8/8			100	0

S. aureus was also recovered from cIAI patients. Table 20 provides the data from the ME population from the integrated cIAI trials (studies 301 and 306) for the MSSA and MRSA isolates combined. Tables 21 and 22 show clinical results for methicillin-susceptible and –resistant *S. aureus* respectively. As can be seen the majority of isolates were from the cIAI patients were MSSA (Table 21). There were only 5 MRSA isolates from cIAI patients (Table 22). The overall bacteriological eradication rate for MSSA and MRSA with a tigecycline MIC of ≤ 0.5 µg/mL was 91% (29/32).

Table 20

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Table 4.2.1.1-3: Microbiological Response and MIC Distribution for the ME Population from the Integrated cIAI Trials for *S. aureus* Isolates

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total ^a	Cumulative % of total isolates	Cumulative % of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.12	17/17	53.1	58.6	100	0
0.25	11/14	96.9	96.6	78.6	21.4
0.5	1/1	100	100	100	0
Total	29/32			91.0	13.3

^a For all MICs the clinical response identical to the microbiological response.

Table 21

Table 4.2-1: Microbiological Response and MIC Distribution for the ME Population from the Integrated cIAI Trials for *S. aureus* Isolates- MSSA

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative % of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.12	16/16	59.3	64.0	100	0
0.25	8/10	96.3	96.0	80	20
0.5	1/1	100	100	100	0
Total	25/27			92.6	7.4
ME-monomicrobic					
0.12	3/3	50.0	50.0	100	0
0.25	3/3	100	100	100	0
Total	6/6			100	0
ME-polymicrobic					
0.12	13/13	61.9	68.4	100	0
0.25	5/7	95.2	94.7	71.4	28.6
0.5	1/1	100	100	100	0
Total	19/21			90.5	9.5

Table 22

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Table 4.2-2: Microbiological Response and MIC Distribution for the ME Population from the Integrated cIAI Trials for *S. aureus* Isolates- MRSA

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative % of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections ^a					
0.12	1/1	20.0	25.0	100	0
0.25	3/4	100	100	75.0	25.0
Total	4/5			80.0	20.0

^a all of the MRSA in cIAI were isolated from polymicrobial infections

CONCLUSION – *STAPHYLOCOCCUS AUREUS*

Based on the fact that the Applicant provided clinical data for only *S. aureus* and that is the organism that they have indicated they want the indication for the tigecycline interpretive criteria will be only for *S. aureus* and not *Staphylococcus* spp.

Based on the clinical data for both the cSSSI and cIAI studies there were only one experience in treating a patient in the cSSSI study that had a *S. aureus* with a tigecycline MIC of 1 µg/mL. It can not be recommended based on this data that the tigecycline MIC interpretive breakpoint for *S. aureus* is (b)(4). In addition, there was no data presented by the Applicant where the tigecycline MIC for *S. aureus* was (b)(4), therefore an intermediate and resistant MIC interpretive breakpoint can not be chosen. There were, however, a number of cases of patients in the clinical studies who had *S. aureus* isolates with a tigecycline MIC of ≤0.5 µg/mL (143 patients in the cSSSI and 32 patients in the cIAI studies). The bacteriological eradication rate for the *S. aureus* in the cSSSI studies with a tigecycline MIC of ≤0.5 µg/mL was 87% (143/165) and for the cIAI study the bacteriological eradication rate was 91% (29/32). Also, because in vitro susceptibility test data indicate that there is no major difference in the tigecycline MIC for either methicillin- susceptible or resistant *S. aureus* and the clinical data support that methicillin-resistant *S. aureus* infections respond to tigecycline it is recommended that the indication be for *S. aureus* (including methicillin-resistant isolates). The recommended tigecycline MIC interpretive breakpoint for *S. aureus* (including methicillin-resistant isolates) is ≤0.5 µg/mL = susceptible.

In the microbiology data for cSSSI the Applicant did not provide information on community-acquired *S. aureus* infections.

STREPTOCOCCI

In Vitro Activity of Tigecycline against Preclinical and Clinical Isolates for *Streptococcus* spp. other than *Streptococcus pneumoniae*

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The Applicant in this submission is requesting that *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus anginosus* group (*Streptococcus anginosus*, *Streptococcus intermedius* and *S. constellatus*) be included in the cSSSI indication. They are suggesting that the tigecycline MIC breakpoint for *Streptococcus* spp. other than *S. pneumoniae* be set a (b) (4)/mL = susceptible. Because of a lack of clinical data for *Streptococcus* spp. with a tigecycline MIC >1 µg/mL they are not requesting an intermediate or resistant breakpoint, which is appropriate.

Table 23 shows the cumulative frequency of tigecycline for *Streptococcus* spp. other than *S. pneumoniae* for preclinical and clinical isolates. As can be seen the tigecycline MICs were somewhat lower for the preclinical isolates. This can be seen also in Figures 6 and 7.

Table 23

Table 4.2.1.2-1: Cumulative frequency of Tigecycline Susceptibility of <i>Streptococcus</i> spp. other than <i>S. pneumoniae</i> isolates from Preclinical and Clinical Tests.									
Cumulative % of susceptible isolates at MIC [N]	MIC (µg/mL)								
	0.004	0.008	≤0.015, 0.015	≤0.03, 0.03	0.06	0.12	0.25	0.5	1
Preclinical [291] *			34.0	76.6	100.0				
Clinical [537]	0.2	0.6	1.5	5.4	78.6	95.3	99.1	99.8	100.0
Total [828]	0.1	0.4	12.9	30.4	86.1	97.0	99.4	99.9	100.0

*Preclinical data for *S. pyogenes* and *S. agalactiae* only

Figures 6 and 7 show the tigecycline MIC distributions for isolates of *S. pyogenes* and *S. agalactiae* from the preclinical and clinical data. The data for *S. pyogenes* and *S. agalactiae* are from the cSSSI and cIAI modified intent to treat populations. As can be seen the highest tigecycline MIC was 0.25 µg/mL for both *S. pyogenes* (2 clinical isolates) and *S. agalactiae* (8 clinical isolates) from the clinical studies.

Figure 6

Figure 4.2.1.2-2: Pre-Clinical and Clinical Frequency Distribution of Tigecycline Minimal Inhibitory Concentrations ($\mu\text{g/ml}$) Against *Streptococcus pyogenes* (N= 176,116)

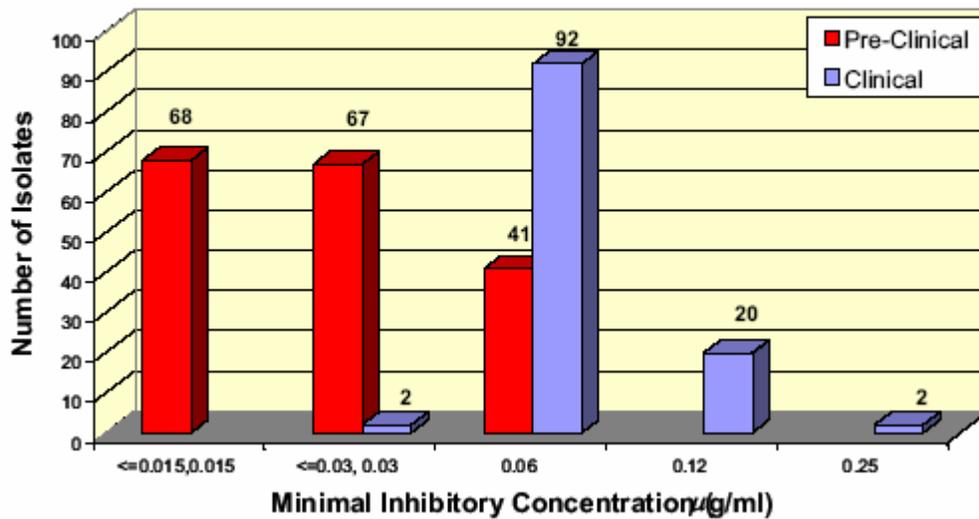


Figure 7

Figure 4.2.1.2-1: Preclinical and Clinical Frequency Distribution of Tigecycline Minimal Inhibitory Concentrations ($\mu\text{g/ml}$) Against *Streptococcus agalactiae* (N= 115,56)

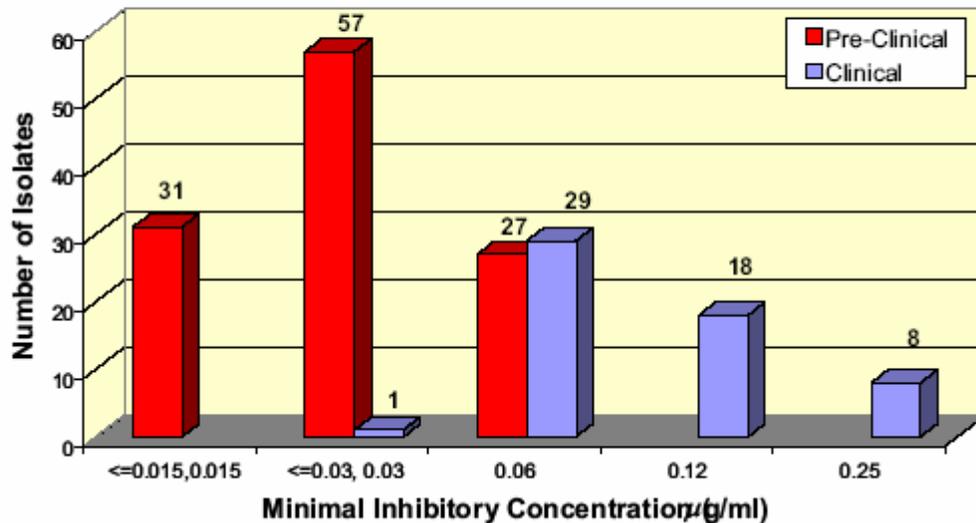


Table 24 shows the distribution of individual *Streptococcus* species associated with microbiologic eradication as defined by the ME population for integrated cSSSI (studies 300 and 305). As can be seen there was limited experience from the clinical trials in treating skin infections due to *S. agalactiae* or due to *S. anginosus*, *S. constellatus* or *S. intermedius*. There was substantial experience with treating skin infections due to *S. pyogenes*. The Applicant is requesting that the organisms *S. anginosus*, *S. constellatus* and *S. intermedius* be included under the cSSSI indication as *Streptococcus anginosus*

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group. cSSSI clinical studies showed that there was a 94% (30/32) bacteriological eradication when the tigecycline MIC for *S. pyogenes* was ≤ 0.25 $\mu\text{g/mL}$. For *S. agalactiae* the bacteriological cure rate when the tigecycline MIC was ≤ 0.25 $\mu\text{g/mL}$ was 88% (7/8). Therefore it is felt that it would be appropriate to include in the package insert a MIC interpretive breakpoint for *S. pyogenes* and *S. agalactiae* of ≤ 0.25 $\mu\text{g/mL}$ = susceptible. For *S. anginosus grp.* with a tigecycline MIC of ≤ 0.25 $\mu\text{g/mL}$ there was a 85% (17/20) bacteriological eradication rate.

Table 24

Table 4.2.1.2-2: Distribution of Individual *Streptococcus* Species Associated with Microbiological Eradication as Defined by the ME Population for Integrated cSSSI

Tigecycline Susceptibility MIC ($\mu\text{g} / \text{mL}$)	<i>S. pyogenes</i>	<i>S. agalactiae</i>	<i>S. anginosus</i>	<i>S. constellatus</i>	<i>S. intermedius</i>
0.008					1/1
0.015					
0.03			1/1		
0.06	22/23	3/3	6/8	1/2 ^a	
0.12	7/8 ^b	2/2	7/7		
0.25	1/1	2/3 ^c	1/1		
0.5					
Total	30/32	7/8	15/17	1/2	1/1

^a The clinical response for *S. constellatus* at 0.06 $\mu\text{g/mL}$ was 0/2.

^b The clinical response for *S. pyogenes* at 0.12 $\mu\text{g/mL}$ was 8/8.

^c The clinical response for *S. agalactiae* at 0.25 $\mu\text{g/mL}$ was 3/3.

The Applicant is proposing that the *Streptococcus anginosus* group (*S. anginosus*, *S. constellatus*, and *S. intermedius*) be included as a pathogen for the cIAI indication. Clinically this group of organisms has been characterized by a propensity for invasive pyogenic infections, which readily differentiate them from the other viridans streptococci (17,18). Microbiologically, members of this group are recognized by their microaerophilic or anaerobic growth requirements, and their formation of minute colonies (19). The bacteriological eradication rate and MIC distribution for the ME population from the cIAI trials for *S. anginosus* group are shown in Table 25. In the ME population of 118 isolates belonging to the *S. anginosus* group only 12 isolates are representative of the monomicrobial population (10/10 at 0.06 $\mu\text{g/mL}$ and 1/2 at 0.12 $\mu\text{g/mL}$). When the tigecycline MIC for the *S. anginosus* group was ≤ 0.25 $\mu\text{g/mL}$ the bacteriological eradication rate was 86% (102/118).

Table 25

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Table 4.2.1.2-4: Microbiological Response and MIC Distribution for the ME population from the cIAI Trials for *Streptococcus anginosus* group.

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative # of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.008	1/1	0.8	1.0	100	0
0.015	2/2	2.5	2.9	100	0
0.03	4/4 ^a	5.9	6.9	100	0
0.06	79/91 ^b	83.1	84.3	86.8	13.2
0.12	15/18	98.3	99.0	83.3	16.7
0.25	1/2	100	100	50	50
Total	102/118			86.4	13.6

^a The clinical response at 0.03 µg/mL was 3/4.

^b The clinical response at 0.06 µg/mL was 78/91. For all other MICs the clinical response was identical the microbiological response.

CONCLUSION – STREPTOCOCCI

Based on the information provided by the Applicant from in vitro preclinical susceptibility testing of tigecycline against streptococci and clinical data from the cSSSI and cIAI studies the following recommendations are made. There will be a tigecycline MIC interpretive breakpoint for *S. pyogenes*, *S. agalactiae*, and *Streptococcus anginosus* group (*S. anginosus*, *S. constellatus*, *S. intermedius*). That MIC interpretive breakpoint will be ≤0.25 µg/mL = susceptible. Because there was no clinical experience in treating cSSSI caused by either *S. pyogenes*, *S. agalactiae* or *S. anginosus* grp. with tigecycline MICs >0.25 µg/mL no intermediate or resistant MIC breakpoint can be established based on the data.

ENTEROCOCCI

In Vitro Activity of Tigecycline against Preclinical and Clinical Isolates for Enterococcus spp.

The Applicant in this submission has only presented an analysis for enterococci based on vancomycin-susceptible strains of *Enterococcus faecalis* since this is the only species of *Enterococcus* for which they are seeking a clinical indication for tigecycline for both the cSSSI and cIAI indications. The Applicant is proposing a tigecycline MIC breakpoint for *E. faecalis* of (b) (4) = susceptible, (b) (4) = indeterminate, and (b) (4) = resistant.

Table 26 provides the overall susceptibility of *E. faecalis* to tigecycline. The distribution of tigecycline MIC for vancomycin-susceptible isolates of *E. faecalis* from the modified microbial intent to treat population including isolates from both treatment groups of the integrated cSSSI and cIAI are shown in Table 26.

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Table 26

Table 4.2.1.3-1: Cumulative frequency of Tigecycline Susceptibility of <i>E. faecalis</i> Isolates From Preclinical and Clinical Tests.							
Cumulative % of susceptible isolates at MIC [N]	MIC (µg/mL)						
	0.03	0.06	0.12	0.25	0.5	1	2
Preclinical [159]	20.8	71.7	94.3	100.0			
Clinical [249]		10.0	75.5	99.2	99.6	99.6	100.0
Total [408]	8.1	34.1	82.8	99.5	99.8	99.8	100.0

Table 27 presents the microbiological eradications for the ME population from the cIAI studies for patients with *E. faecalis* (the Applicant has indicated that these are all vancomycin-susceptible). cIAI clinical studies showed that for vancomycin-susceptible *E. faecalis* a tigecycline MIC of 0.12 µg/mL correlated with a 77% (13/17) bacteriological eradication rate. As can be seen a tigecycline MIC of 0.25 µg/mL correlated with 85% (11/13) bacteriological eradication rate. The bacteriological eradication rate for vancomycin-susceptible *E. faecalis* with a tigecycline MIC of ≤0.25 µg/mL was 81% (26/32) in the cIAI population. The majority of the cIAI study population was composed of polymicrobial infections there was only 1 monomicrobial infection (1 organism eradicated at 0.06 µg/mL).

Table 27

Table 4.2.1.3-2: Microbiological Response and MIC Distribution for the ME Population from the Integrated cIAI Trials for *E. faecalis* Isolates

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative % of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.06	2/2	6.3	7.7	100	0
0.12	13/17	59.4	57.7	76.5	23.5
0.25	11/13 ^a	100	100	84.6	15.4
Total	26/32			81.3	18.8

^a The clinical response at 0.25 µg/mL was 10/13. For all other MICs the clinical response was identical to the microbiological response.

Table 28 presents the microbiological eradications from the ME populations for the cSSSI studies for patients with *E. faecalis*. The data in Table 28 is for all infections, and polymicrobial infections. There were only two patients with monomicrobial infections (one eradication each at 0.12 µg/mL and 0.25 µg/mL). cSSSI clinical studies showed that for vancomycin-susceptible *E. faecalis* a tigecycline MIC of ≤0.25 µg/mL correlated with

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an 88% (14/16) bacteriological eradication rate. It can be seen that the cSSSI results as related to the tigecycline MICs are similar to the tigecycline MICs for the *E. faecalis* seen in the cIAI studies.

Table 28

Table 4.2.1.3-3: Microbiological Response and MIC Distribution for the ME Population from the Integrated cSSSI Trials for *E. faecalis* Isolates

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative % of isolates associated with microbiological eradications	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.12	10/12 ^a	75	71.4	83.3	16.7
0.25	4/4 ^b	100	100	100	0
Total	14/16			87.5	12.5
ME-polymicrobial					
0.12	9/11	78.6	75	81.8	18.2
0.25	3/3	100	100	100	0
Total	12/14			85.7	14.3

^a The clinical response at 0.12 µg/mL was 9/12.

^b The clinical response at 0.25 µg/mL was 3/4. For all other MICs the clinical response was identical to the microbiological response.

CONCLUSION – *ENTEROCOCCUS FAECALIS*

Because *E. faecalis* can be a cause of cSSSI and cIAI and studies have shown it to be susceptible to tigecycline and that tigecycline showed a good eradication rate during clinical trials it is appropriate to include this organism in both indications. The MIC interpretive criteria that would be appropriate for *Enterococcus faecalis* (vancomycin-susceptible isolates only) is ≤0.25 µg/mL = susceptible. Because there was no clinical experience in with vancomycin-susceptible *E. faecalis* with tigecycline MICs >0.25 µg/mL there will be no intermediate or resistant MIC interpretive criteria. Since clinical data was only provided for *E. faecalis* the header for the in vitro susceptibility interpretive criteria is more appropriately *Enterococcus faecalis* (vancomycin susceptible isolates only) rather than [REDACTED]^{(b) (4)}, as proposed by the Applicant.

ENTEROBACTERIACEAE

In Vitro Activity of Tigecycline against Preclinical and Clinical Isolates for Enterobacteriaceae

The Applicant is proposing that for the cIAI indication that *C. freundii*, *E. cloacae*, *E. coli*, *K. oxytoca*, and *K. pneumoniae* be included as the target pathogens. They are also proposing that *E. coli* alone be included as a target pathogen in the cSSSI indication.

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The analysis presented by the Applicant for *Enterobacteriaceae* in this submission is based on five members of the *Enterobacteriaceae* family. These are *E. coli*, *K. pneumoniae*, *K. oxytoca*, *E. cloacae*, and *C. freundii*. The Applicant is proposing a MIC breakpoint of ≤ 2 $\mu\text{g/mL}$ = susceptible, 4 $\mu\text{g/mL}$ = intermediate, and ≥ 8 $\mu\text{g/mL}$ = resistant.

Table 29 presents the overall susceptibility of *Enterobacteriaceae* to tigecycline. The data include *C. freundii*, *E. cloacae*, *K. oxytoca*, *K. pneumoniae* and *E. coli*. As can be seen 99.3% of these organisms are susceptible to ≤ 2 $\mu\text{g/mL}$ of tigecycline.

Table 29

Table 4.2.1.4-1: Tigecycline Susceptibility of <i>Enterobacteriaceae</i> Isolates From Preclinical and Clinical Datasets.									
Cumulative % of susceptible isolates at MIC	MIC ($\mu\text{g/mL}$)								
	0.03	0.06	0.12	0.25	0.5	1	2	4	8
Preclinical [848]	0.7	4.2	20.9	60.1	92.7	98.1	99.4	99.6	100.0
Clinical [1829]		0.5	10.6	58.4	87.4	97.8	99.2	99.7	100.0
Total [2677]	0.2	1.7	13.8	58.9	89.1	97.9	99.3	99.7	100.0

Figure 8 shows a histogram of the frequency of distribution of MICs for all *Enterobacteriaceae* (preclinical and clinical including organisms others than *E. coli*, *K. pneumoniae*, *K. oxytoca*, *E. cloacae*, and *C. freundii*). Figures 9 shows the frequency of distribution of MICs overlaid with the preclinical MIC distribution for the combination of the individual species *E. coli*, *K. pneumoniae*, *K. oxytoca*, *E. cloacae*, and *C. freundii*. Figures 10 – 14 are histograms of the frequency distribution MICs for *C. freundii*, *E. cloacae*, *E. coli*, *K. oxytoca*, and *K. pneumoniae*,

Figure 8

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Figure 4.3.3-14: Preclinical and Clinical Frequency Distribution of Tigecycline Minimal Inhibitory Concentrations ($\mu\text{g/ml}$) Against All *Enterobacteriaceae* (N= 2597,2136)

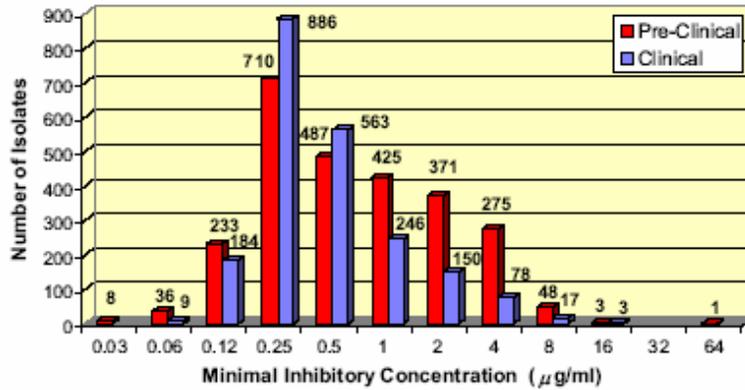


Figure 9

Figure 4.3.3-15: Preclinical and Clinical Frequency Distribution of Tigecycline Minimal Inhibitory Concentrations ($\mu\text{g/ml}$) Against *Enterobacteriaceae* (*C. freundii* Complex, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*) Organisms for Clinical Indications (N= 848,1829)

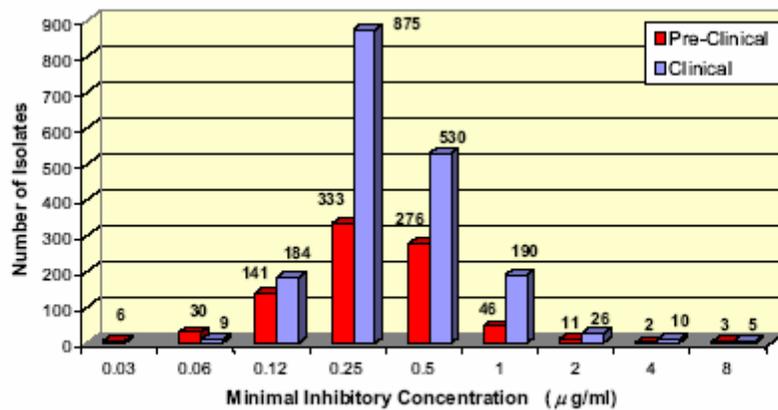


Figure 10

Figure 4.3.3-16: Preclinical and Clinical Frequency Distribution of Minimal Inhibitory Concentrations ($\mu\text{g/ml}$) Against *Citrobacter freundii* Complex (N= 160,47)

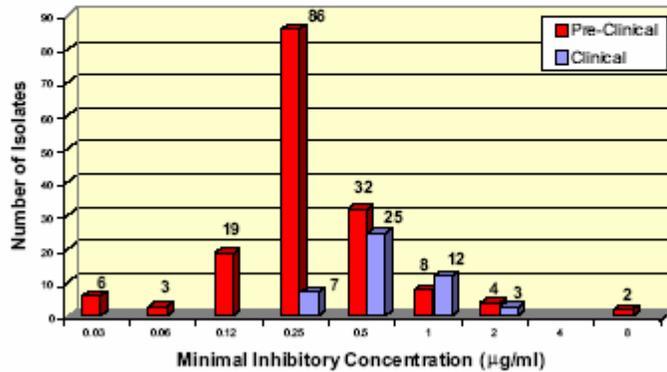


Figure 11

Figure 4.3.3-17: Preclinical and Clinical Frequency Distribution of Tigecycline Minimal Inhibitory Concentrations ($\mu\text{g/ml}$) Against *Enterobacter cloacae* (N= 160,115)

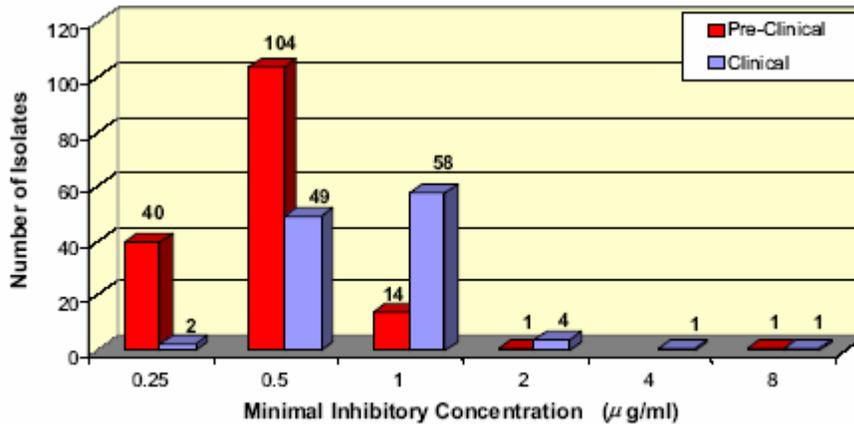


Figure 12

Figure 4.3.3-18: Preclinical and Clinical Frequency Distribution of Minimal Inhibitory Concentrations ($\mu\text{g/ml}$) Against *Escherichia coli* (N= 208,1311)

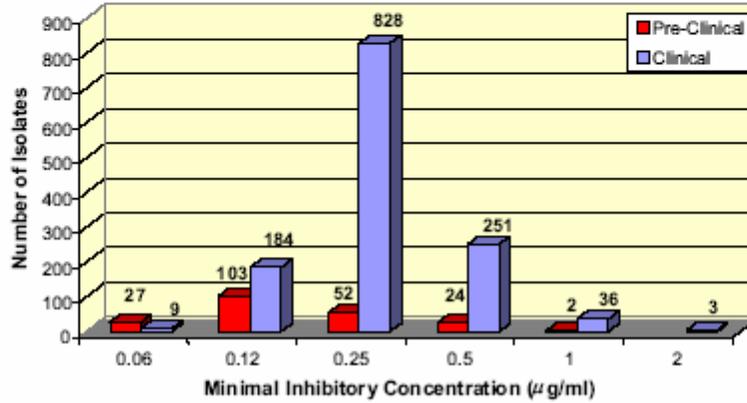


Figure 13

Figure 4.3.3-19: Preclinical and Clinical Frequency Distribution of Tigecycline Minimal Inhibitory Concentrations ($\mu\text{g/ml}$) Against *Klebsiella oxytoca* (N= 140,87)

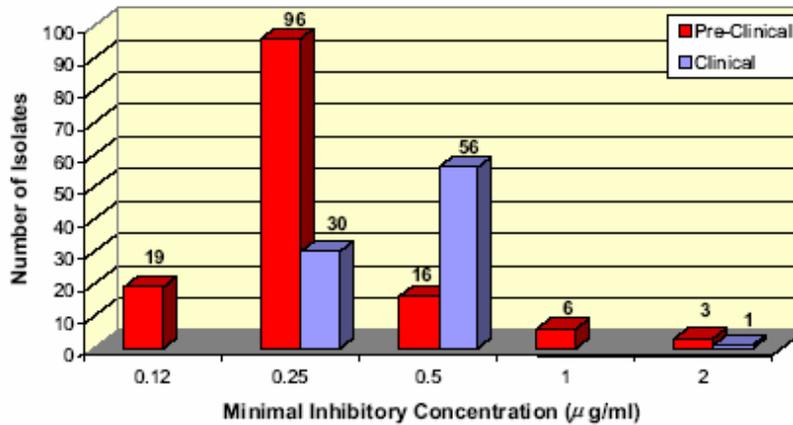


Figure 14

Figure 4.3.3-20: Preclinical and Clinical Frequency Distribution of Tigecycline Minimal Inhibitory Concentrations ($\mu\text{g/ml}$) Against *Klebsiella pneumoniae* (N= 180,269)

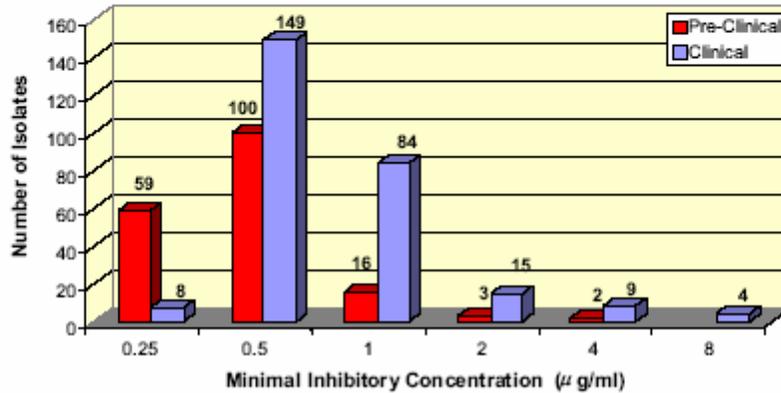


Table 30 shows the microbiological eradications from the ME population from cIAI studies for the *Enterobacteriaceae* grouping. The data is presented for all the infections, monomicrobial and polymicrobial ME populations. The data show that when the tigecycline MIC for an *Enterobacteriaceae* isolates was $\leq 2 \mu\text{g/mL}$ the bacteriological eradication rate was 86% (370/428). When the tigecycline MIC for an *Enterobacteriaceae* isolate was $\leq 1 \mu\text{g/mL}$ the bacteriological eradication rate was also 86% (361/421). A similar distribution of susceptibility to tigecycline is observed in the mono and polymicrobial populations.

Table 30

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Table 4.2.1.4-2: Microbiological Response and MIC Distribution for the ME Population from the Integrated cIAI Trials for *Enterobacteriaceae* Isolates

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative% of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all infections					
0.06	2/3	0.7	0.5	66.7	33.3
0.12	31/37 ^a	9.3	8.9	83.8	16.2
0.25	199/228 ^b	62.5	62.5	87.3	12.7
0.5	103/118	90.0	90.3	87.3	12.7
1	28/35	98.1	97.8	80.0	20.0
2	7/7	99.8	99.7	100	0
4	1/1	100	100	100	0
Total	371/429		100	86.5	13.5
ME-monomicrobial					
0.06	0	0	0	0	0
0.12	13/14	12.0	12.0	92.9	7.1
0.25	66/70	71.8	73.1	94.3	5.7
0.5	23/25	93.2	94.4	92.0	8.0
1	4/6	98.3	98.1	66.7	33.3
2	2/2	100	100	100	7.7
Total	108/117			92.3	

Table 4.2.1.4-2: Microbiological Response and MIC Distribution for the ME Population from the Integrated cIAI Trials for *Enterobacteriaceae* Isolates

Tigecycline Susceptibility MIC (µg/mL)	Microbiological response N eradications/N total	Cumulative % of total isolates	Cumulative% of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-polymicrobial					
0.06	2/3	1.0	0.8	66.7	33.3
0.12	18/23	8.3	7.6	78.3	21.7
0.25	133/158	59.0	58.2	84.2	15.8
0.5	80/93	88.8	88.6	86.0	14.0
1	24/29	98.1	97.7	82.8	17.2
2	5/5	99.7	99.6	100	0
4	1/1	100	100	100	0
Total	263/312			84.3	

Clinical response is given for each pathogen in Table 4.2.1.4-3.

Table 31 presents the microbiological results for the ME population for each genus of *Enterobacteriaceae* from the cIAI trials. As seen in the table there was experience during the clinical trials with 10 or more of the various genera. The overall bacteriological eradication rate for these specific *Enterobacteriaceae* when the tigecycline MIC was ≤ 2

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µg/mL was 86% (370/428). Bacteriological eradication rates for the specific *Enterobacteriaceae* when the tigecycline MIC was ≤ 1 µg/mL ranged from 71% to 100%. There was very little clinical experience with individual *Enterobacteriaceae* that had a tigecycline MIC of ≥2 µg/mL.

Table 31

Table 4.2.1.4-3: Distribution of Individual *Enterobacteriaceae* Associated with Microbiological Eradication as Defined by the ME Population for Integrated cIAI

Tigecycline Susceptibility MIC (µg /mL)	<i>C. freundii</i>	<i>E. cloacae</i>	<i>K. oxytoca</i>	<i>E. coli</i>	<i>K. pneumoniae</i>
0.06				2/3	
0.12				31/37 ^a	
0.25	3/3		7/7	188/217 ^b	1/1
0.5	5/7	9/9	12/13	54/63	23/16
1	2/4	5/7		5/5	16/19
2	2/2				5/5
4					1/1
Total	12/16	14/16	19/20	280/325	46/52

^a The clinical response for *E. coli* at 0.12 µg/mL was 30/37.

^b The clinical response for *E. coli* at 0.25 µg/mL was 187/217.

The Applicant also provides data to support their request to include *E. coli* as a target pathogen in the cSSSI indication. Table 32 shows the overall susceptibility of *E. coli* to tigecycline. Here it can be seen that 97.3% of the total isolates (preclinical and clinical) are inhibited at a tigecycline MIC of ≤0.5 µg/mL and basically 100% are inhibited by an MIC of ≥1 µg/mL.

Table 32

Table 4.2.1.4-4: Tigecycline Susceptibility of <i>E. coli</i> Isolates From Preclinical and Clinical Tests.						
Cumulative % of susceptible isolates at MIC	MIC (µg/mL)					
	0.06	0.12	0.25	0.5	1	2
Preclinical [208]	13.0	62.5	87.5	99.0	100.0	100.0
Clinical [1311]	0.7	14.7	77.9	97.0	99.8	100.0
Total [1519]	2.4	21.3	79.2	97.3	99.8	100.0

Table 33 shows the microbiological eradications for the ME population from cSSSI studies for patients with *E. coli*. As can be seen a tigecycline MIC of ≤1 µg/mL was associated with bacteriological eradication rate of 83% (24/29).

Table 33

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Table 4.2.1.4-5: Microbiological Response and MIC Distribution for the ME Population from the Integrated cSSSI Trials for *E. coli* Isolates

Tigecycline Susceptibility MIC ($\mu\text{g/mL}$)	Microbiological response N eradicatio ns/N total	Cumulative % of total isolates	Cumulative % of isolates associated with microbiological eradications at each MIC	% of isolates associated with microbiological eradication at each MIC	% of isolates associated with microbiological persistence at each MIC
ME-all					
0.12	5/6	20.7	85.9	88.3	16.7
0.25	14/16 ^a	75.9	88.2	87.5	12.5
0.5	4/6	96.6	66.7	66.7	33.3
1	1/1	100	100	100	0
Total	24/29			82.8	17.2
ME-monomicrobial					
0.12	3/4	40	37.5	75	25
0.25	2/2	60	62.5	100	0
0.5	2/3	90	87.5	66.7	33.3
1.0	1/1	100	100	100	0
Total	8/10			80.0	20
ME-polymicrobial					
0.12	2/2	10.5	12.5	100	0
0.25	12/14	84.2	87.5	85.7	14.3
0.5	2/3	100	100	66.7	33.3
Total	16/19			84.2	15.8

^a The clinical response at 0.25 $\mu\text{g/mL}$ was 15/16. For all other MICs the clinical response was identical to the microbiological response.

Tigecycline Activity against Proteus sp., Providencia sp., and Morganella spp.

The Applicant has indicated in this submission that certain *Enterobacteriaceae* namely *Proteus sp.*, *Providencia sp.*, and *Morganella sp.* have decreased susceptibility to tigecycline (section 2.7.4.2 subsection 1.4.2.2). Figure 15 shows the shift of the tigecycline MIC for *P. mirabilis* to less susceptible than MICs for *C. freundii*, *E. cloacae*, *K. oxytoca*, *K. pneumoniae*, and *E. coli* (see Figures 8-14). Figure 16 shows the tigecycline shift to less susceptible for *Morganella morganii* than for *C. freundii*, *E. cloacae*, *K. oxytoca*, *K. pneumoniae*, and *E. coli*. Because of the decreased susceptibility of these organisms to tigecycline the Applicant is not asking to have any of them included in the package insert for tigecycline.

Figure 15

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Figure 4.3.1-28: MIC vs. Microbiological response for cSSSI-ME population; Mono and Polymicrobial Infections compared with Preclinical Population Distribution form *Proteus mirabilis*

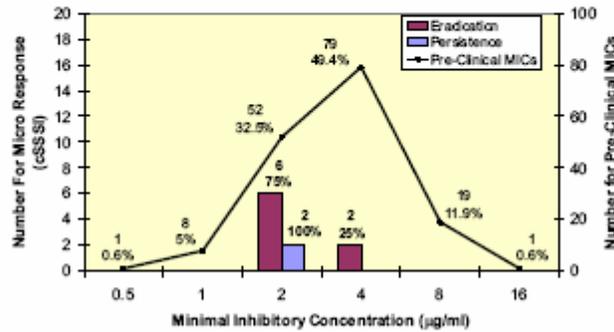
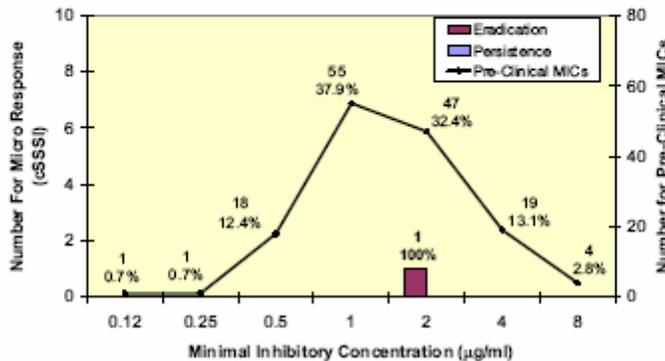


Figure 16

Figure 4.3.1-27: MIC vs. Microbiological response for cSSSI-ME population; Mono and Polymicrobial Infections compared with Preclinical Population Distribution for *Morganella morganii*



Development of Resistance to Tigecycline during Clinical Studies

During the clinical trials (Phase 2 and 3) there were incidences of the development of decreased susceptibility (MIC \geq 4 µg/mL) to tigecycline while the patient was receiving tigecycline (see Table 34). In total there were six organisms from five patients that had decreased susceptibility. All of the isolates were documented to be identical to the baseline isolate by ribotyping. There were two patients with *K. pneumoniae*, and one patient each that had *E. aerogenes*, *Acinetobacter calcoaceticus/baumanni*, and *M.*

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morganii. In addition, there was one patient that had an *E. coli* isolate for which the tigecycline MIC increased from 0.5 to 2 µg/mL (not shown in Table 32).

Table 34

Table 1.4.2.4-3: Clinical isolates that Developed decreased susceptibility While on therapy with tigecycline ^{8, 11, 13-24}

Wyeth Accession	Organism	(b) (4) Accession	Protocol	Patient	Date of Isol.	TGC MIC (µg/mL)	Ribotype	Clin. Resp.	Treatment ^a	Comments
587	<i>Enterobacter aerogenes</i>	P895062			3-Apr-01	0.25	XVIII			Developed on therapy
666	<i>Enterobacter aerogenes</i>	C974083	202	26	27-Apr-01	4	XVIII	failure	TGC	Developed on therapy
6913	<i>Klebsiella pneumoniae</i>	N599317			16-Mar-04	0.5	CDLXXXVII			
6914	<i>Klebsiella pneumoniae</i>	N599343			16-Mar-04	0.5	CDLXXXVII			
7003	<i>Klebsiella pneumoniae</i>	N599359			16-Mar-04	0.5	CDLXXXVII			
7004	<i>Klebsiella pneumoniae</i>	N599322			16-Mar-04	0.5	CDLXXXVII			
7398	<i>Klebsiella pneumoniae</i>	N651337			16-Mar-04	1	CDLXXXVII			
7399	<i>Klebsiella pneumoniae</i>	N651319			16-Mar-04	0.5	CDLXXXVII			
7186	<i>Klebsiella pneumoniae</i>	N640033			21-Mar-04	1	CDLXXXVII			
7187	<i>Klebsiella pneumoniae</i>	N640050			21-Mar-04	2	CDLXXXVII			
7397	<i>Klebsiella pneumoniae</i>	N651282			21-Mar-04	1	CDLXXXVII			
7338	<i>Klebsiella pneumoniae</i>	N640071			24-Mar-04	1	CDLXXXVII			Developed on therapy
7188	<i>Klebsiella pneumoniae</i>	N643219	306	2074	28-Mar-04	8	CDLXXXVII	failure	TGC	Developed on therapy
7608	<i>Klebsiella pneumoniae</i>	K575255			11-May-04	0.5	DCLVII			Developed on therapy
7609	<i>Klebsiella pneumoniae</i>	K227255	307	127	12-May-04	4	DCLVII	cure	blinded	Developed on therapy
7457	<i>Klebsiella pneumoniae</i>	C444360			27-Mar-04	2	DCLXX			All isolates identical except for one strain.
7293	<i>Klebsiella pneumoniae</i>	C444347			29-Mar-04	8	DCLXX			MICs of identical isolates tested as 2 or 8 µg/mL on alternating days
7140	<i>Klebsiella pneumoniae</i>	C554297			29-Mar-04	0.5	DCLXIX			
7629	<i>Klebsiella pneumoniae</i>	C444329			31-Mar-04	2	DCLXX			
7630	<i>Klebsiella pneumoniae</i>	C565162			3-Apr-04	8	DCLXX			
7679	<i>Klebsiella pneumoniae</i>	C565115	309	2181	19-Apr-04	2	DCLXX	Cure	TGC	Developed on therapy
4904	<i>A. calcoacet./baumanni comp.</i>	I219585			14-Dec-03	2	CDXLV			
5141	<i>A. calcoacet./baumanni comp.</i>	L412314			19-Dec-03	2	CDXLV			
5140	<i>A. calcoacet./baumanni comp.</i>	L412374			21-Dec-03	8	CDXLV			Developed on therapy
5139	<i>A. calcoacet./baumanni comp.</i>	L412385	309	526	30-Dec-03	16	CDXLV	cure	TGC	Developed on therapy

In addition there were patients who acquired organisms with a decreased susceptibility to tigecycline while on tigecycline (Table 35). There were eight patients with *K. pneumoniae*, two with *E. cloacae*, and one with *S. marcescens*. As can be seen 2 of the 11 patients were successfully treated.

Table 35

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Table 1.4.2.4-2: Clinical isolates that had decreased susceptibility that were acquired on therapy. ^{8, 11, 13-24}

Wyeth Accession	Organism	(b) (4)		Date of Isol.	TGC MIC	Ribotype	Clin. Resp.	Treatment ^f	Comments
		Accession	Protocol Patient		(µg/mL)				
7593	<i>Enterobacter cloacae</i>	Y757743	301 123	16-Apr-03	8	ND ^a	cure	TGC	no susceptible isolate at baseline
7875	<i>Enterobacter cloacae</i>	L604744	307 201	19-May-04	4	ND	failure		no susceptible isolate at baseline
5288	<i>Serratia marcescens</i>	K512640	306 875	4-Dec-03	8	ND	cure	IMI	no susceptible isolate at baseline
340	<i>Klebsiella pneumoniae</i>	P471332	200 349	8-Oct-00	16	ND	cure	TGC	no susceptible isolate at baseline
2332	<i>Klebsiella pneumoniae</i>	K453670	306 1809	16-May-03	2	ND	cure	IMI	no susceptible isolate at baseline
2532	<i>Klebsiella pneumoniae</i>	B969121	305 2087	20-Jun-03	4	ND	cure	TGC	no susceptible isolate at baseline
3721	<i>Klebsiella pneumoniae</i>	L718130		24-Sep-03	0.5	NGA ^b			resistant strains different ribotype from baseline.
4408	<i>Klebsiella pneumoniae</i>	L987180		30-Sep-03	4	CCXIV			Patient acquired second strain type which was resistant
4103	<i>Klebsiella pneumoniae</i>	L718220		7-Oct-03	4	CCXIV			
4409	<i>Klebsiella pneumoniae</i>	L916670	305 269	22-Oct-03	0.5	NGA	cure	TGC	no susceptible isolate at baseline
4433	<i>Klebsiella pneumoniae</i>	L916450	305 273	23-Oct-03	4	ND	cure	TGC	no susceptible isolate at baseline
4467	<i>Klebsiella pneumoniae</i>	L971520	305 1570	9-Oct-03	4	ND	cure	TGC	no susceptible isolate at baseline
7396	<i>Klebsiella pneumoniae</i>	J300025	301 1213	15-Apr-04	4	ND	failure	TGC	no susceptible isolate at baseline
5701	<i>Klebsiella pneumoniae</i>	K279535	309 576	25-Jan-04	4	ND	cure	TGC	no susceptible isolate at baseline

^a ND, not done because only one isolate of that genus and species was obtained from the patient

^b NGA, no group assigned

^c Treatment group. TGC, tigecycline; IMI, imipenem/cilastatin;

CONCLUSION – *ENTEROBACTERIACEAE* (*C. FREUNDII*, *E. CLOACAE*, *K. OXYTOCA*, *E. COLI*, and *K. PNEUMONIAE*)

It is appropriate to include *C. freundii*, *E. cloacae*, *K. pneumoniae*, *K. oxytoca* and *E. coli* as target pathogens in the cIAI indication. *E. coli* is an organism that can be associated with cSSSI therefore it is felt that this organism should be included as a target pathogen in the cSSSI indication. From the preclinical and clinical in vitro susceptibility test data for the aforementioned organisms, pharmacokinetic/pharmacodynamic parameters of tigecycline and bacteriological eradication data/clinical outcome data from clinical trials the interpretive breakpoints of $\leq 2 \mu\text{g}/\text{ml}$ = susceptible, $4 \mu\text{g}/\text{ml}$ = intermediate and $(b) (4) \mu\text{g}/\text{ml}$ = resistance would be appropriate for *Enterobacteriaceae* defined as *C. freundii*, *E. cloacae*, *K. pneumoniae*, *K. oxytoca*, and *E. coli*.

The Applicant is not asking to have any species of *Proteus*, *Morganella* or *Providencia* included in the package insert for tigecycline because of their decreased susceptibility to tigecycline. It is recommended that the following statement be included in the package insert “Tigecycline has reduced in vitro activity in against *Proteus* species, *Morganella* species, and *Providencia* species”.

ANAEROBES – Clinical Experience

The Applicant is requesting that in the cSSSI indication that only *Bacteroides fragilis* be included. However, it is very rarely a sole etiological agent but rather a part of a polymicrobial infection. In the case of the indication for cIAI the Applicant is requesting that the organisms *B. fragilis*, *B. thetaiotaomicron*, *B. uniformis*, *B. vulgatus*, *C. perfringens*, and *P. micros* be included. All of these organisms can be found in the

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intestines and are commonly found in intraabdominal infections as part of a polymicrobial mixture.

The numbers in Table 36 are too small from the cSSSI clinical studies to make a valid decision of what concentration of tigecycline is actually effective in treating cSSSI infections where there is the presence of *B. fragilis*. The data from the cSSSI studies showed that there was a 100% (5/5) bacteriological eradication rate and 80% (4/5) clinical cure rate when the *B. fragilis* had a tigecycline MIC of 0.5 µg/mL. Clinical experience with tigecycline treating cSSSI infections where the tigecycline MIC was > 0.5 µg/mL was basically nonexistent.

Table 36

cIAI clinical studies (Table 37) showed that there was a 68% bacteriological eradication of *B. fragilis* and a 100% bacteriological eradication of *B. thetaiotaomicron* and *C. perfringens* when they had a tigecycline MIC of 1 µg/mL. When the *B. fragilis* had a MIC of 1 µg/mL there was a clinical cure rate of 65%. When the tigecycline MIC was ≤4 µg/mL the bacteriological eradication rate for the anaerobes in Table 37 was 84% (158/189). It can be seen in Table 4.2.1.5-3 that when the tigecycline MIC for *B. fragilis*, *B. uniformis* or *B. thetaiotaomicron* was 16 µg/mL there was 100% bacteriological eradication there was 50% clinical cure in the case of *B. fragilis* and no clinical cure in the case of *B. uniformis*. The bacteriological eradication rate was the lowest for *B. fragilis* (77% - 56/73) and *P. micros* (76% - 13/17).

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Table 37

Table 4.2.1.5-3: Distribution of Individual Anaerobes Associated with Microbiological Eradication as Defined by the ME Population for Integrated cIAI

Tigecycline Susceptibility MIC (µg /mL)	<i>B. fragilis</i>	<i>B. thetaiotaomicron</i>	<i>B. vulgatus</i>	<i>B. uniformis</i>	<i>C. perfringens</i>	<i>P. micros</i>
0.06			5/5	2/3	6/6	12/16
0.12	2/2	5/8	2/2	4/4	4/5	1/1
0.25	14/16	6/7	3/3	3/4 ^a	2/2	
0.5	19/24	10/10	3/5	4/4	2/2	
1	21/31 ^a	8/8			2/2	
2	7/8	4/4 ^c			2/2	
4	2/2	1/1	1/1	1/1 ^e		
8	2/2	1/1				
16	2/2 ^b	2/2		1/1 ^f		
Total	69/87	37/41	14/16	15/17	18/19	13/17

^a The clinical response for *B. fragilis* at 1.0 µg/mL was 20/31.

^b The clinical response for *B. fragilis* at 16 µg/mL was 1/2.

^c The clinical response for *B. thetaiotaomicron* at 2.0 µg/mL was 3/4.

^d The clinical response for *B. uniformis* at 0.25 µg/mL was 2/4.

^e The clinical response for *B. uniformis* at 4.0 µg/mL was 0/1.

^f The clinical response for *B. uniformis* at 16.0 µg/mL was 0/1.

CONCLUSION – ANAEROBES (*B. FRAGILIS*, *B. THETAIOAOMICRON*, *B. VULGATUS*, *B. UNIFORMIS*, *C. PERFRINGENS*, AND *P. MICROS*)

The Applicant is requesting that in the cSSSI indication that only *Bacteroides fragilis* be included. This is appropriate because this organism can be associated with complicated skin and skin structure infection. However, it is very rarely a sole etiological agent but rather a part of a polymicrobial infection. In the case of the indication for cIAI the Applicant is requesting that coverage for anaerobes be based on the cIAI data for *B. fragilis*, *B. thetaiotaomicron*, *B. uniformis*, *B. vulgatus*, *C. perfringens*, and *P. micros*. All of these organisms can be found in the intestines along with other anaerobes and these anaerobes are commonly found in intraabdominal infections as part of a polymicrobial mixture. Therefore it is appropriate to include these organisms in the cIAI indication. Based on MIC₉₀ data and clinical experience it would appear that appropriate tigecycline breakpoints anaerobes would be appropriate MIC interpretive criteria would be ≤4 µg/mL = susceptible, 8 µg/mL = intermediate and ≥16 µg/mL = resistant.

IN VITRO SUSCEPTIBILITY TEST INTERPRETIVE CRITERIA

Proposed by Applicant

The Applicant is proposing the following in vitro susceptibility testing interpretive criteria (Table 38).

Table 38

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Table 4.2.1-1: Proposed Interpretive Criteria For Tigecycline						
Grouping	MIC (µg/mL)			Zone (mm)		
	S	I	R	S	I	R
						(b) (4)
<i>Streptococcus</i> spp. not <i>S. pneumoniae</i>		-	-	≥19	-	-
						(b) (4)
Enterobacteriaceae	≤2	4	≥8	≥19	15-18	≤14
Anaerobes	≤4	8	(b) (4)	NA	NA	NA

Each grouping of organisms will be discussed individually and the Agency proposed interpretive criteria stated.

***Staphylococcus* spp.**

The Applicant in their proposed package insert is requesting that *S. aureus* (methicillin-susceptible and –resistant isolates) be included in the indication for complicated skin and skin structure (cSSSI) and that *S. aureus* (methicillin-susceptible be included in the cIAI indication. Therefore in the in vitro susceptibility section of the package insert it is appropriate for the heading to read “*Staphylococcus aureus* (including methicillin-resistant isolates)”.

Table 38 shows the tigecycline in vitro susceptibility test interpretive criteria be requested by the Applicant.

Figure 17 shows the scattergram when the preclinical in vitro susceptibility data are combined with the clinical in vitro data. Figure 17 includes both methicillin-susceptible and –resistant isolates of *S. aureus*. Figures 18 and 19 show scattergrams constructed from just methicillin-susceptible *S. aureus* (MSSA) isolates and methicillin-resistant *S. aureus* (MRSA) isolates respectively. As can be seen the scattergrams for MSSA and MRSA are similar. The majority of isolates in Figures 17, 18 and 19 with an MIC of ≥ 0.5 µg/mL are preclinical isolates of *S. aureus*.

The Applicant in the submission has provided scattergrams constructed from the in vitro susceptibility data for staphylococci isolated from patients enrolled in the cSSSI and cIAI studies (Figures 20 and 21). Figure 20 shows the scattergram constructed from all the MSSA isolates (monomicrobial and polymicrobial infections) obtained from patients enrolled in the cSSSI studies. Figure 21 shows the scattergram constructed from all the MRSA isolates (monomicrobial and polymicrobial infections) obtained in the cSSSI studies. Figure 22 shows the scattergram constructed from the all MSSA isolates (monomicrobial and polymicrobial infections) obtained from patients in the cIAI studies.

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A MRSA scattergram is not shown for these isolates obtained from cIAI patients because there were only 2 of these isolates. The scattergrams constructed from the cSSSI and cIAI isolates are similar.

Figure 17

Figure 4.2.2.1.1-4: Error rate-bounded analysis for *S. aureus* (MSSA and MRSA), for isolates from m-mITT population of patients from clinical protocols and preclinical data, excluding laboratory mutants.

MIC vs zone plot for preclinical and clinical (IAI and skin) data based on October 25 2004 MIC and zone interpretive criteria
 Staphylococcus spp. (without lab mutants) : Organisms for clinical indications

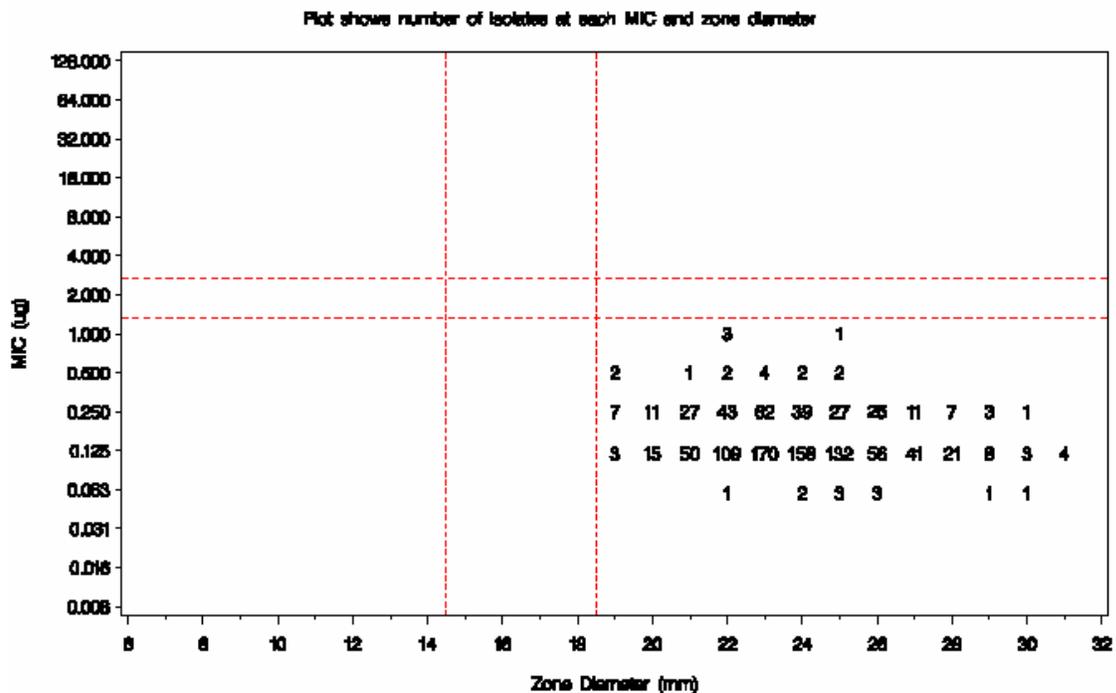


Figure 18

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Figure 5.2-1: Error rate-bounded analysis for *S. aureus* MSSA, for isolates from m-mITT population of patients from clinical protocols and preclinical data excluding laboratory mutants.

MIC vs zone plot for preclinical and clinical (AI and skin) data
 based on proposed MIC and zone interpretive criteria
S. aureus MSSA (without lab mutants) : All organisms

Plot shows number of isolates at each MIC and zone diameter

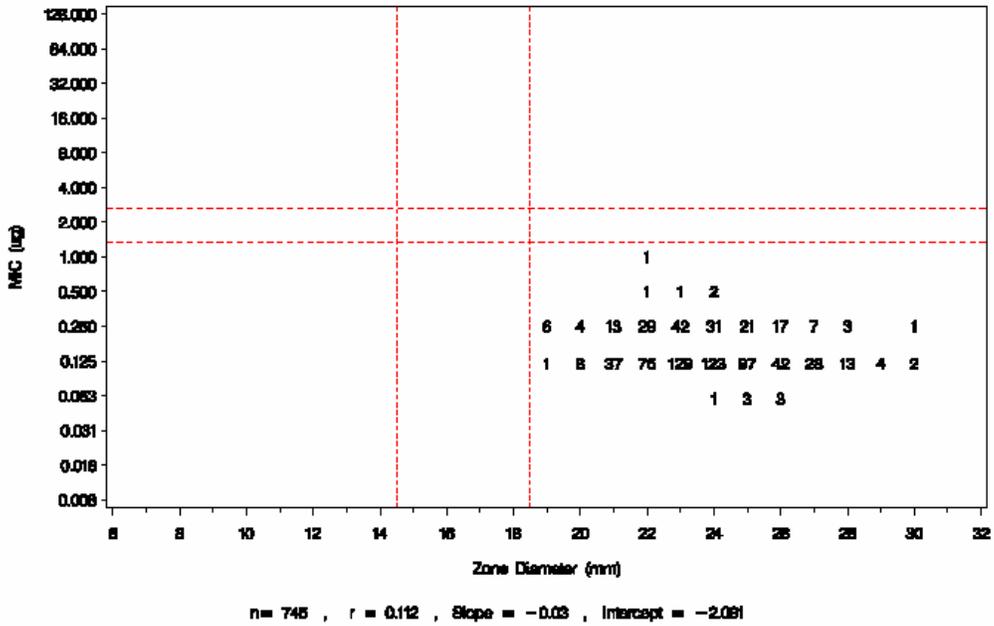


Figure 19

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Figure 5.2-2: Error rate-bounded analysis for *S. aureus* MRSA, for isolates from m-mITT population of patients from clinical protocols and preclinical data excluding laboratory mutants.

MIC vs zone plot for preclinical and clinical (AI and skin) data based on proposed MIC and zone interpretive criteria
S. aureus MRSA (without lab mutants) : All organisms

Plot shows number of isolates at each MIC and zone diameter

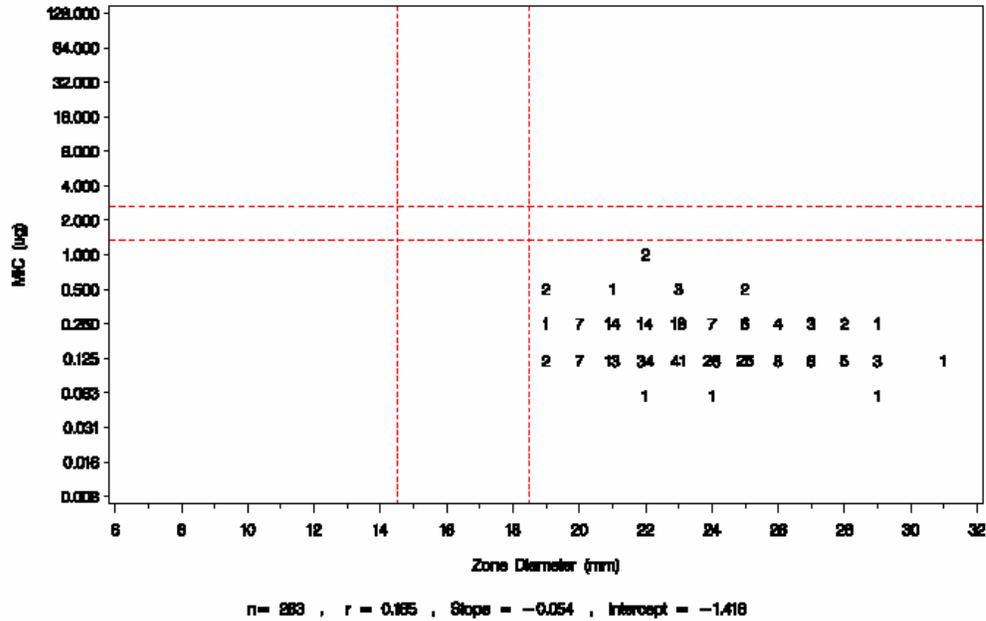


Figure 20

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Figure 6.2-1: Error rate-bounded analysis for *S. aureus* MSSA from skin protocols (300 and 305) based on proposed MIC and zone interpretive criteria, Tigecycline microbiologically evaluable patients with microbiological response = eradication, all infections

MIC vs zone plot for data from skin protocols (300 and 305)
 based on proposed MIC and zone interpretive criteria
 Tigecycline 50 mg microbiologically evaluable patients with microbiological response = eradication
S. aureus MSSA : All infections

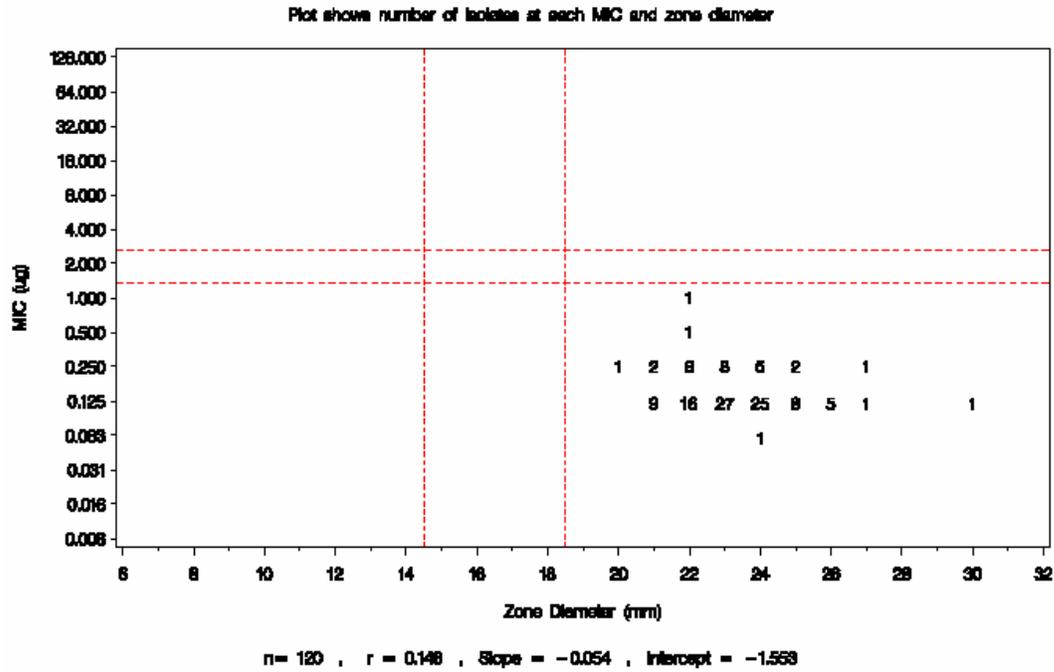


Figure 21

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Figure 6.2-4: Error rate-bounded analysis for *S. aureus* MRSA from skin protocols (300 and 305) based on proposed MIC and zone interpretive criteria, Tigecycline microbiologically evaluable patients with microbiological response = eradication, all infections

MIC vs zone plot for data from skin protocols (300 and 305)
 based on proposed MIC and zone interpretive criteria
 Tigecycline 50 mg microbiologically evaluable patients with microbiological response = eradication
S. aureus MRSA : All infections

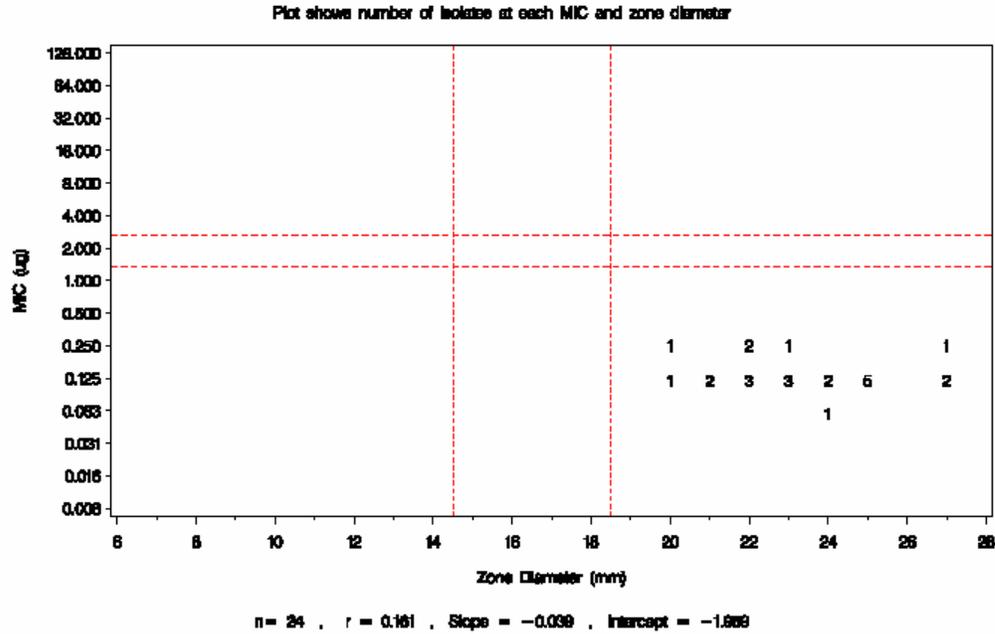


Figure 22

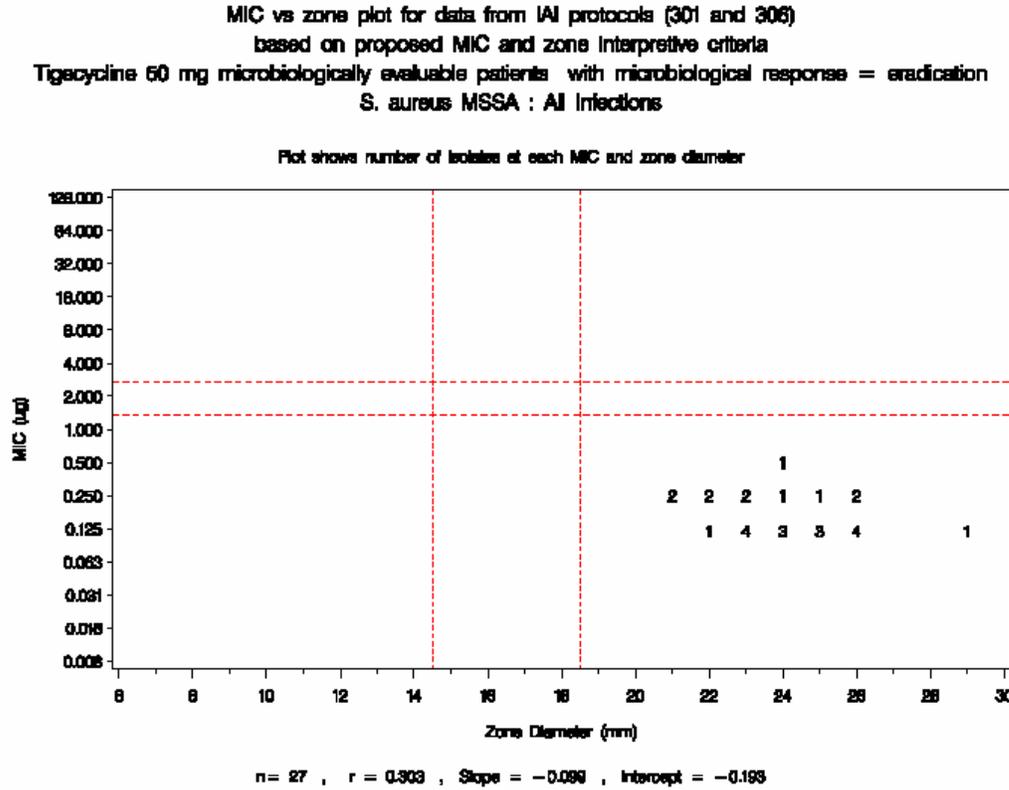
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Figure 6.2-7: Error rate-bounded analysis for *S. aureus* MSSA from IAI protocols (301 and 306) based on proposed MIC and zone interpretive criteria, Tigecycline microbiologically evaluable patients with microbiological response = eradication, all infections



CONCLUSION – *Staphylococcus aureus*

Based on the pharmacokinetic/pharmacodynamic parameters of tigecycline, tigecycline preclinical and clinical susceptibility data, and clinical experience with treating *S. aureus* infections (both methicillin-susceptible and methicillin-resistant infections) the MIC and disc diffusion zone size interpretive criteria proposed by the Agency are seen in Table 39. The lack of indeterminate and resistant interpretive criteria is because there were very few *S. aureus* with an MIC greater than 0.5 µg/mL and there was little experience during clinical trials in treating infections caused by either methicillin-susceptible or –resistant isolates of *S. aureus* that had a tigecycline MIC > 0.25 µg/mL (see Tables 17 and 18).

The Agency proposed interpretive criteria results in a very small very major error (called susceptible by disc diffusion testing and called resistant by MIC testing) of 1.8% when all the isolates from the cSSSI and cIAI studies are added (173) and divided into the 3 isolates that would be called susceptible by disc diffusion testing. This very major rate (0.4%) is well within the <2% value recommended by CLSI (14)

Table 39

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Staphylococcus aureus (including methicillin-resistant isolates)

	<u>MIC ($\mu\text{g/mL}$)</u>	<u>Disc diffusion zone size (mm)</u>
Susceptible	≤ 0.5	≥ 19

Streptococcus spp. not including *S. pneumoniae*

As noted in Table 38 the Applicant is proposing interpretive criteria for *Streptococcus* spp. not including *S. pneumoniae*. They are defining “*Streptococcus* spp.” as *S. pyogenes*, *S. agalactiae*, and the *Streptococcus anginosus* grp. *Streptococcus* grp. includes *S. anginosus*, *S. constellatus*, and *S. intermedius*. The Applicant is requesting that *S. pyogenes* and *S. agalactiae* be included in the cSSSI indication and only the *S. anginosus* group be included in the cIAI indication. The organisms *S. pyogenes* and *S. agalactiae* are organisms commonly associated with cSSSI infections. The *S. anginosus* group of organisms may be associated with cSSSI infections. They usually are isolated as individual organisms along with other organisms. The *S. anginosus* group of organisms is also commonly isolated from intraabdominal infections but they are commonly isolated with a variety of other bacteria also making their role in this infection process unclear. During clinical trials there was experience in treating cSSSI infections and cIAI infections due to the presence of the *S. anginosus* group of organisms (see Tables 24 and 25). The majority of this experience was with *S. anginosus* group organisms being part of a polymicrobial infection. During clinical trials there was also very little experience in treating cSSSI due to *S. agalactiae* (7 cases) while there was considerably more experience in treating cSSSI infections due to *S. pyogenes*.

Figure 23 shows the scattergram constructed from preclinical and clinical isolates of *S. pyogenes*, *S. agalactiae*, *S. anginosus*, *S. constellatus*, and *S. intermedius*. Figure 24 shows the scattergram constructed just from the preclinical and clinical isolates of *S. pyogenes* while Figures 25 and 26 show scattergrams constructed just from the *S. agalactiae* and *S. anginosus* preclinical and clinical isolates respectively. As can be seen the *S. anginosus* group isolates made up the greatest number of the isolates. The *S. anginosus* group isolates also had the organisms (two) with the highest MICs (0.5 $\mu\text{g/mL}$). The scattergrams for the three different organisms are very similar.

Figure 27 is a scattergram constructed from all the isolates (monomicrobial and polymicrobial infections) of *S. pyogenes* obtained from patients in the cSSSI studies while Figures 28 and 29 are scattergrams constructed from all the isolates of *S. agalactiae* and *S. anginosus* group from patients in the cSSSI studies.

The Applicant is not asking for the inclusion of *S. pyogenes* or *S. agalactiae* in the cIAI indication. No *S. agalactiae* isolates were obtained from patients in the cIAI studies while only one isolate of *S. pyogenes* was obtained from a patient in the cIAI studies. They are requesting that *S. anginosus* group be included in the cIAI indication. Figure 30 is a scattergram constructed from isolates obtained from patients in the cIAI studies.

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As can be seen all the scattergrams (Figures 27 – 30) are similar and are similar to the scattergrams constructed from the preclinical and clinical isolates (Figures 23 – 26).

Figure 23

Figure 4.2.2.1.2-2: Error Rate-Bounded Analysis for combined preclinical and clinical (m-mITT population) for *Streptococcus* spp. other than *S. pneumoniae*, organisms for clinical indication (*S. pyogenes*, *S. agalactiae*, *S. anginosus*, *S. constellatus*, *S. intermedius*)

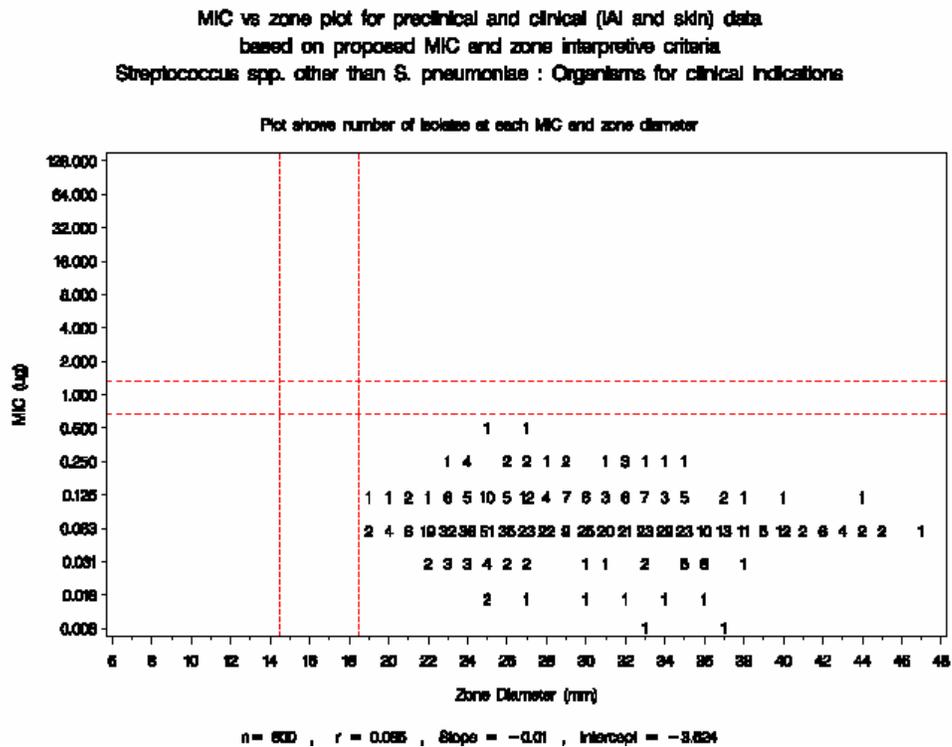


Figure 24

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Figure 7.2-1: Error rate-bounded analysis for *Streptococcus pyogenes* for isolates from m-mITT population of patients from clinical protocols and preclinical data

MIC vs zone plot for preclinical and clinical (AI and skin) data
 based on proposed MIC and zone interpretive criteria
Streptococcus pyogenes : All organisms

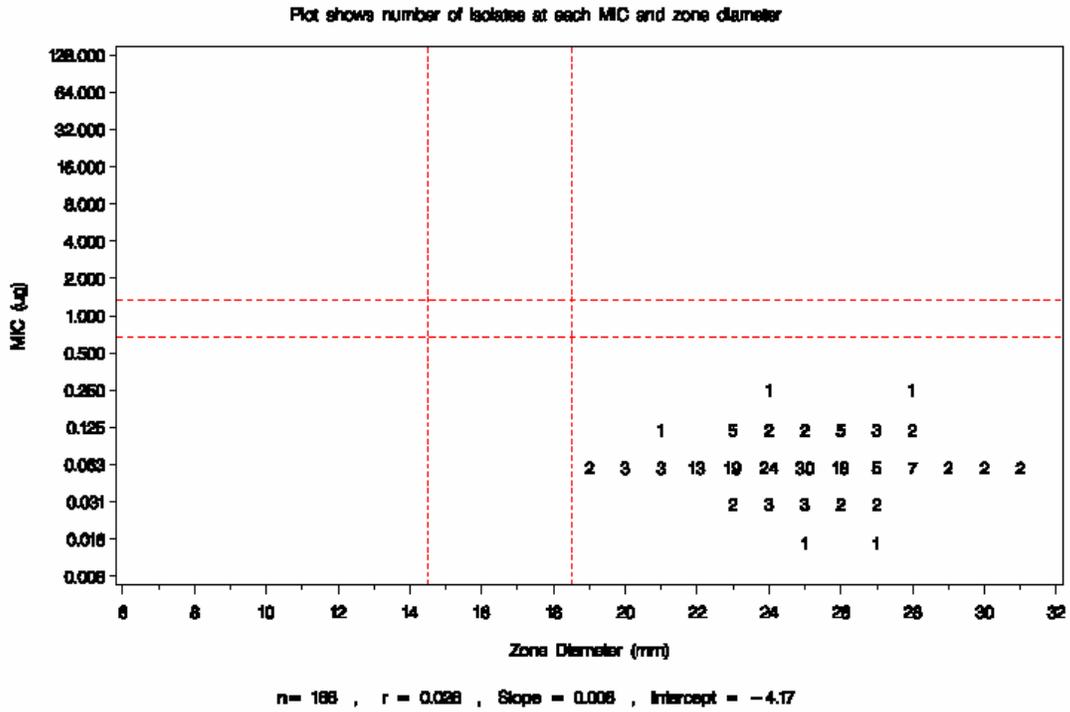


Figure 25

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Figure 7.2-2: Error rate-bounded analysis for *Streptococcus agalactiae* for isolates from m-mITT population of patients from clinical protocols and preclinical data

MIC vs zone plot for preclinical and clinical (AI and skin) data
 based on proposed MIC and zone interpretive criteria
Streptococcus agalactiae : All organisms

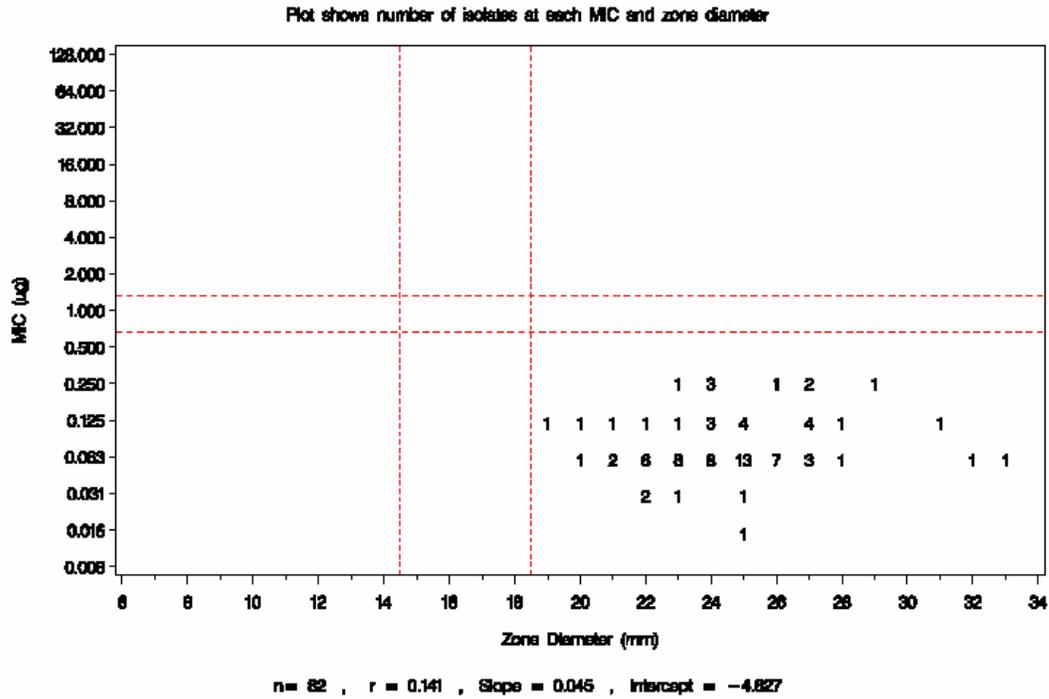


Figure 26

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Figure 7.2-3: Error rate-bounded analysis for *Streptococcus anginosus* group (includes *S. anginosus*, *S. constellatus* and *S. intermedius*) for isolates from m-mITT population of patients from clinical protocols and preclinical data

MIC vs zone plot for preclinical and clinical (AI and skin) data
 based on proposed MIC and zone interpretive criteria
Streptococcus anginosus group : All organisms

Plot shows number of isolates at each MIC and zone diameter

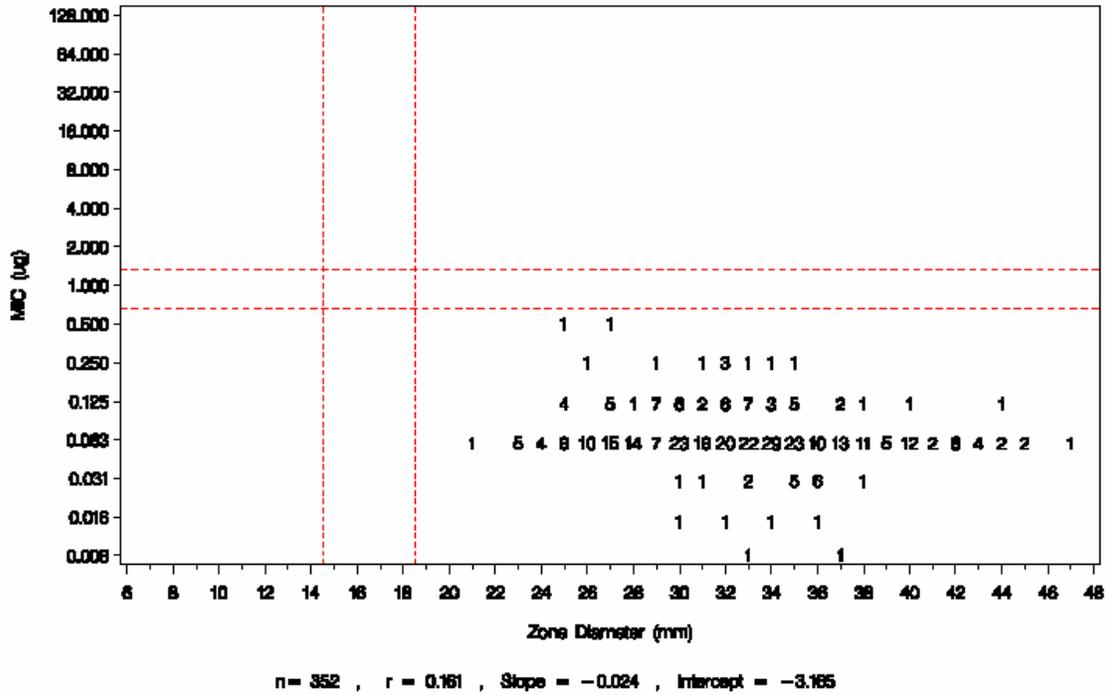


Figure 27

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Figure 8.2-1: Error rate-bounded analysis for *S. pyogenes* from skin protocols (300 and 305) based on proposed MIC and zone interpretive criteria, Tigecycline microbiologically evaluable patients with microbiological response = eradication, all infections

MIC vs zone plot for data from skin protocols (300 and 305)
 based on proposed MIC and zone interpretive criteria
 Tigecycline 50 mg microbiologically evaluable patients with microbiological response = eradication
 Streptococcus pyogenes : All infections

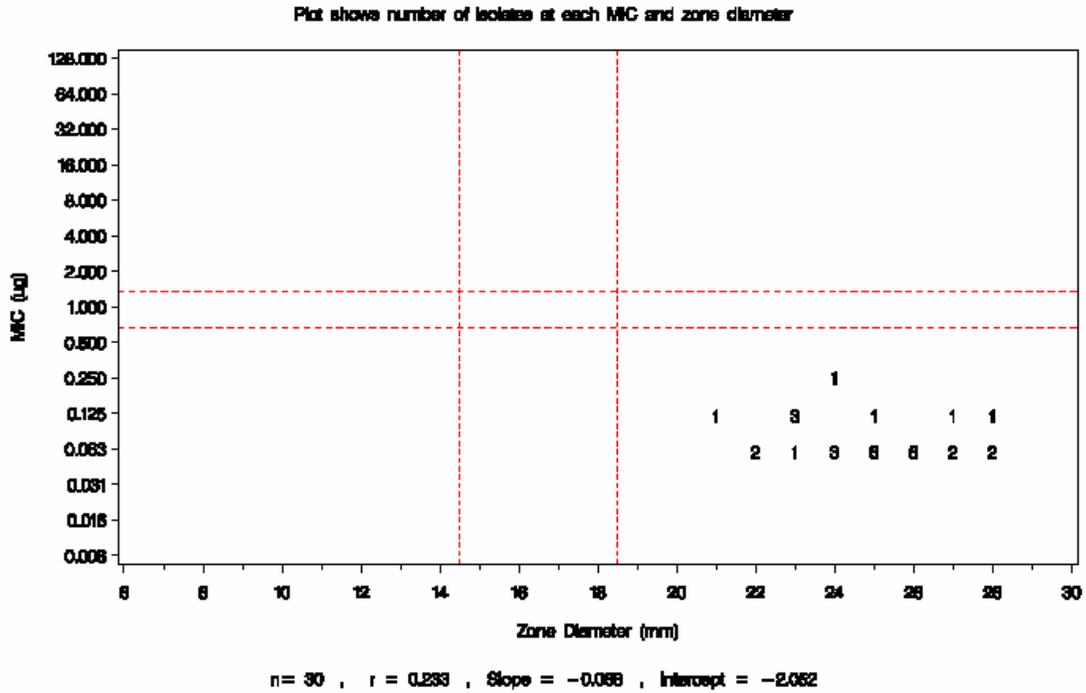


Figure 28

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Figure 8.2-4: Error rate-bounded analysis for *S. agalactiae* from skin protocols (300 and 305) based on proposed MIC and zone interpretive criteria, Tigecycline microbiologically evaluable patients with microbiological response = eradication, all infections

MIC vs zone plot for data from skin protocols (300 and 305)
based on proposed MIC and zone interpretive criteria
Tigecycline 50 mg microbiologically evaluable patients with microbiological response = eradication
Streptococcus agalactiae : All Infections

Plot shows number of isolates at each MIC and zone diameter

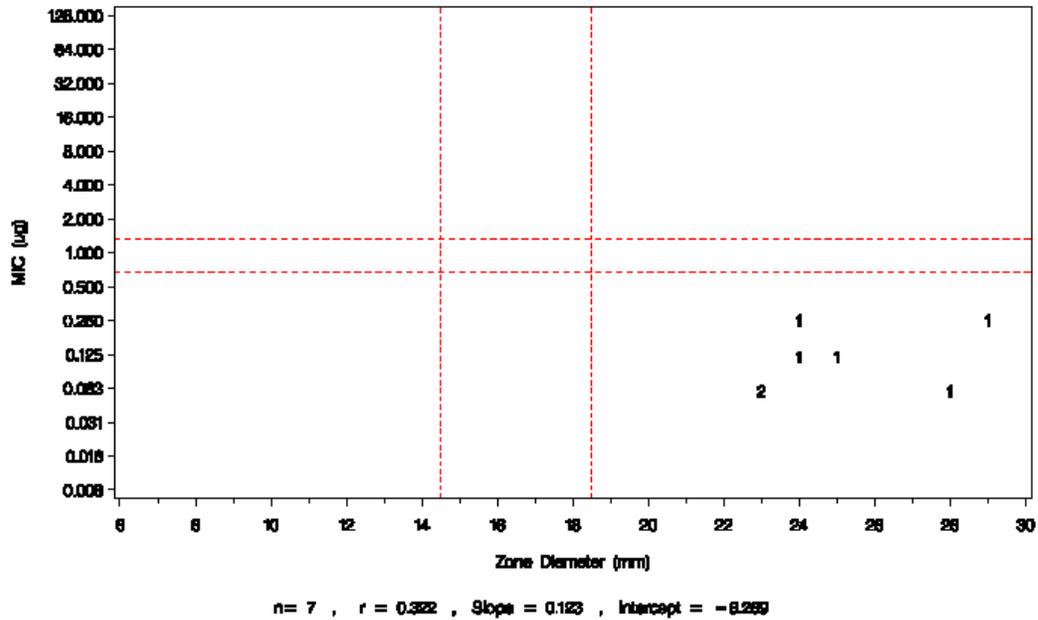


Figure 29

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Figure 8.2-6: Error rate-bounded analysis for *Streptococcus anginosus* group (includes *S. anginosus*, *S. constellatus* and *S. intermedius*) from skin protocols (300 and 305) based on proposed MIC and zone interpretive criteria, Tigecycline microbiologically evaluable patients with microbiological response = eradication, all infections

MIC vs zone plot for data from skin protocols (300 and 305)
 based on proposed MIC and zone interpretive criteria
 Tigecycline 50 mg microbiologically evaluable patients with microbiological response = eradication
 Streptococcus anginosus group : All infections

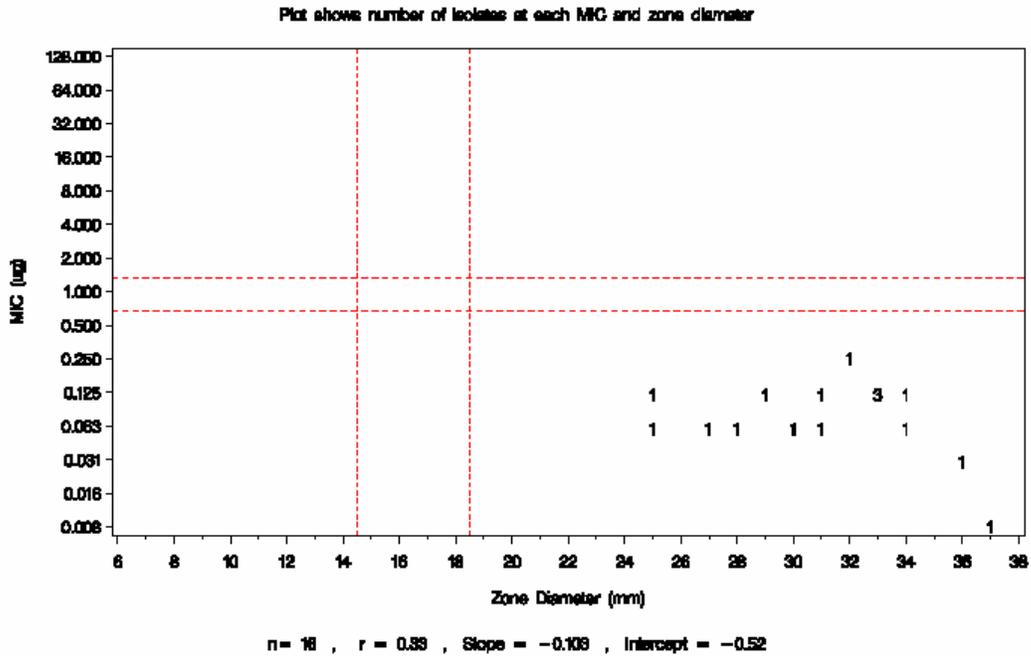


Figure 30

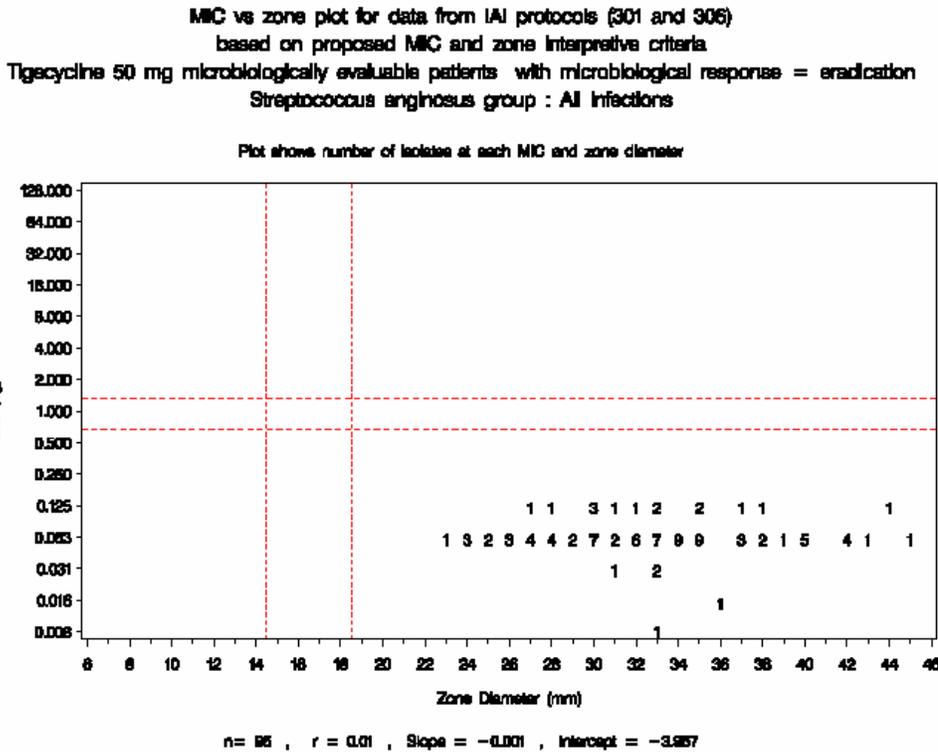
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Figure 8.2-11: Error rate-bounded analysis for *Streptococcus anginosus* group (includes *S. anginosus*, *S. constellatus* and *S. intermedius*) from IAI protocols (301 and 306) based on proposed MIC and zone interpretive criteria, Tigecycline microbiologically evaluable patients with microbiological response = eradication, all infections



CONCLUSION – Streptococci

There was clinical experience treating cSSSI infections due to *S. pyogenes* and *S. agalactiae*. In the case of cIAI infections there was clinical experience caused by the *S. anginosus* group of organisms during clinical trials with tigecycline. These organisms can be represented in the interpretive breakpoint table as *Streptococcus* spp. other than *S. pneumoniae*. The *S. anginosus* group (*S. anginosus*, *S. constellatus* and *S. intermedius*) are members of the viridians streptococcus group. Table 40 shows the Agency’s proposed interpretive criteria for these organisms.

Table 40

Streptococcus agalactiae, *Streptococcus pyogenes* and *S. anginosus* group (*S. anginosus*, *S. constellatus*, *S. intermedius*) –*Streptococcus* spp. other than *S. pneumoniae*

	<u>MIC (µg/mL)</u>	<u>Disc diffusion zone size (mm)</u>
Susceptible	≤0.25	≥19

***Enterococcus* spp.**

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During clinical trials there was very little experience in either the cSSSI or cIAI studies with treating infections in which *E. faecalis* was the sole pathogen (2 in the cSSSI study and 1 in the cIAI study). See Table 27 and 28 of this review. NOTE: only two of the three isolates had both MIC and disk diffusion susceptibility test results. The remaining experience was when the *E. faecalis* was part of a mixed population of organisms (polymicrobial infection). All of the *E. faecalis* isolates were vancomycin susceptible. Because *E. faecalis* can be a pathogen associated with cSSSI and cIAI infections it is appropriate to have this organism (vancomycin- susceptible isolates) included under the cSSSI and cIAI indications.

As can be seen in Table 38 the Applicant is proposing that interpretive criteria for (b) (4) be included in the tigecycline package insert. For the cSSSI and cIAI indications they are requesting only *Enterococcus faecalis* (vancomycin susceptible isolates only). Therefore the header for the interpretive criteria will be “*Enterococcus faecalis*” (vancomycin susceptible isolates only).

Figure 31 shows the scattergram constructed from *E. faecalis* preclinical in vitro susceptibility data and in vitro susceptibility data of *E. faecalis* isolates obtained from patients in the cSSSI and cIAI studies. Figure 32 is a scattergram constructed from the tigecycline in vitro susceptibility data of the *E. faecalis* (all isolates were vancomycin susceptible) obtained from patients in the cSSSI with monomicrobial or polymicrobial infections (all infections). Figure 33 shows a scattergram constructed from the *E. faecalis* (all isolates were vancomycin-susceptible) susceptibility data for isolates obtained from patients in the cIAI study. The scattergram is for all infections [polymicrobial and monomicrobial (only two data points)]. As can be seen there is considerably more susceptibility data in Figure 33. Figure 33 was constructed from in vitro MIC and disc diffusion susceptibility results for *E. faecalis* isolated from patients in the cIAI study.

Figure 31

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Figure 4.2.2.1.3-3 Error rate-bounded analysis for *Enterococcus faecalis* for isolates from m-mITT population of patients from clinical protocols and preclinical data

MIC vs zone plot for preclinical and clinical (AI and skin) data based on October 25 2004 MIC and zone interpretive criteria
 Enterococcus spp. : Organisms for clinical indications

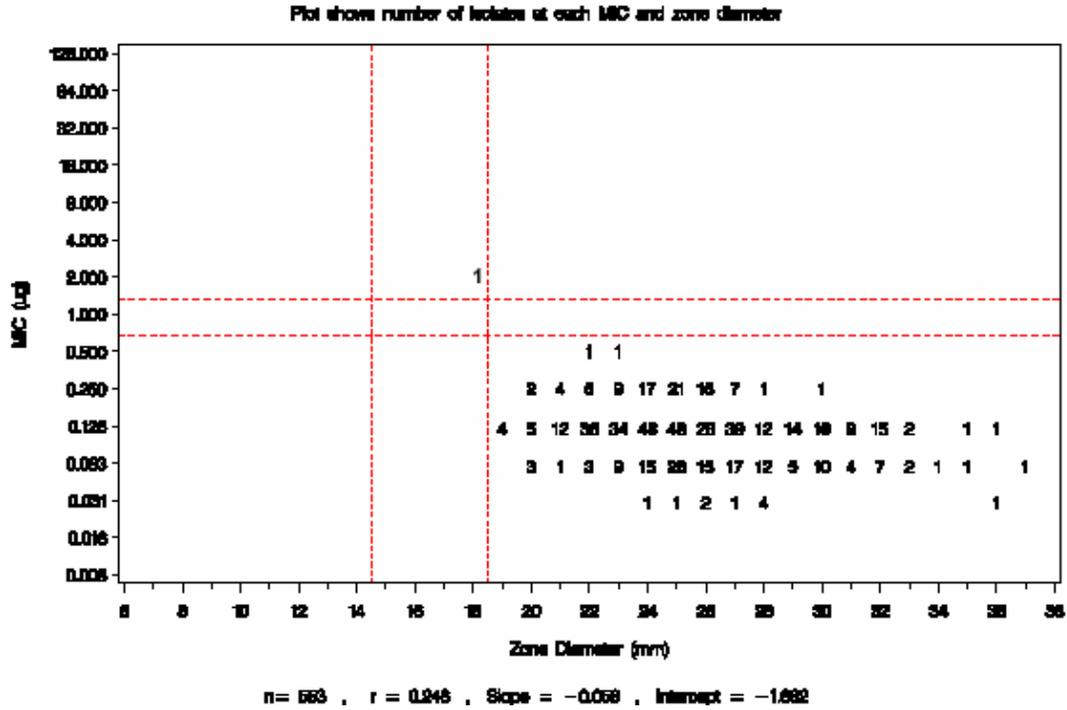


Figure 32

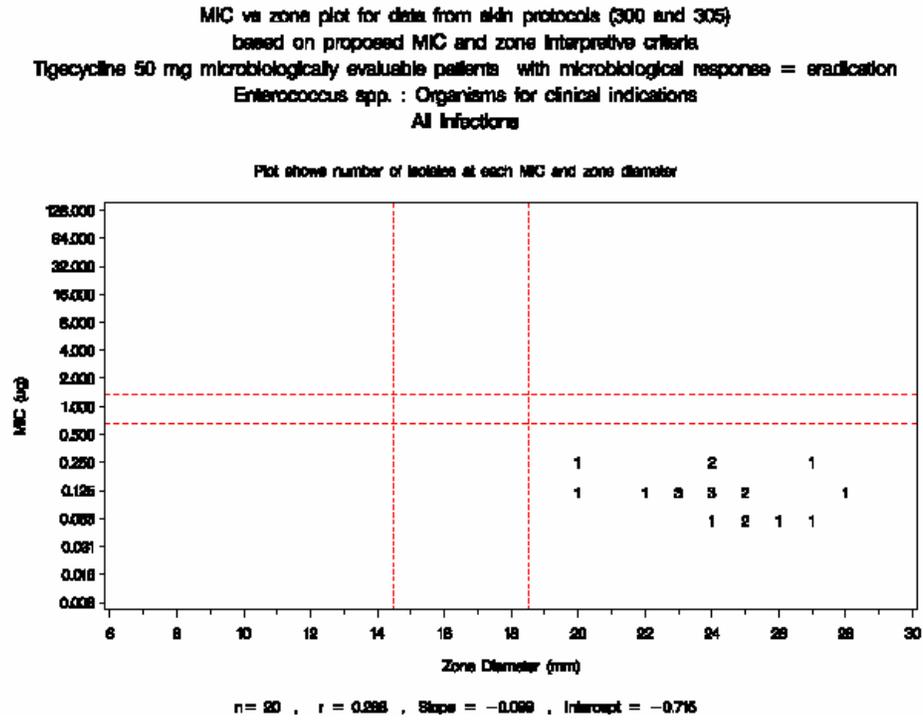
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NDA 21-821

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Figure 4.2.2.1.3-6: Error rate-bounded analysis for data from skin protocols (300 and 305) based on proposed MIC and zone interpretive criteria, Tigecycline microbiologically evaluable patients with microbiological response = eradication, *Enterococcus* spp.: Organisms for clinical indications (*E. faecalis*) All infections



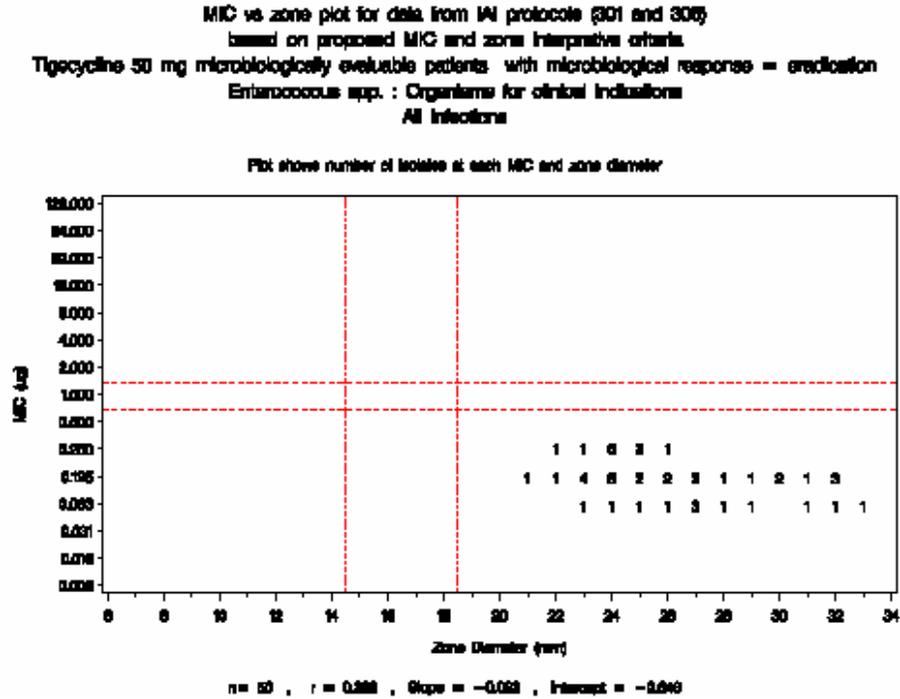
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Figure 4.2.2.2.3-6: Error rate-bounded analysis for data from IAI protocols (301 and 306) based on proposed MIC and zone interpretive criteria, Tigecycline microbiologically evaluable patients with microbiological response = eradication, *Enterococcus* spp. : Organisms for clinical indications, (*E. faecalis*), All infections



CONCLUSION – *Enterococcus faecalis* (vancomycin-susceptible)

Based on the data in Figures 31, 32, and 33 a MIC breakpoint of $\leq 0.25 \mu\text{g/mL}$ with a disc diffusion breakpoint of $\geq 19 \text{ mm}$ = susceptible seems appropriate for *E. faecalis* (vancomycin-susceptible isolates). No intermediate or resistant interpretive categories are necessary because of the paucity of data with isolates that have a tigecycline MIC of greater than $0.12 \mu\text{g/mL}$.

Enterobacteriaceae

As seen in Table 38 the Applicant is requesting that for the in vitro susceptibility test section that the term *Enterobacteriaceae* be used as a header. The genera and species on which the Applicant has provided clinical study data are *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, and *Klebsiella pneumoniae*. Tigecycline has reduced activity against certain members of the *Enterobacteriaceae*. These members are *Proteus* spp., *Providencia* spp., and *Morganella* spp. Therefore, a footer will be added to the interpretive table to state that tigecycline has reduced activity in vitro against *Morganella* spp., *Proteus* spp., and *Providencia* spp. For the cSSSI indication the Applicant is requesting the inclusion only of *E. coli*.

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Figure 34 shows the scattergram constructed from preclinical in vitro susceptibility data for *C. freundii*, *E. cloacae*, *E. coli*, *K. oxytoca*, and *K. pneumoniae* and in vitro susceptibility for the same organisms obtained during cSSSI and cIAI studies. Figure 35 shows the scattergram for the isolates of *C. freundii*, *E. cloacae*, *E. coli*, *K. oxytoca*, and *K. pneumoniae* associated with all cIAI (polymicrobial and monomicrobial). Figure 36 shows the scattergram constructed from susceptibility test results for *C. freundii*, *E. cloacae*, *E. coli*, *K. oxytoca*, and *K. pneumoniae* associated with all cSSSI (polymicrobial and monomicrobial). As can be seen from the scattergrams in Figures 34 – 36 the distribution of susceptibility data is very similar. The in vitro susceptibility test interpretive criteria for broth dilution and disk diffusion testing that the Applicant is proposing for *Enterobacteriaceae* are seen in Table 41.

Table 41. Tigecycline in vitro susceptibility test interpretive criteria for *C. freundii*, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*

MIC (µg/mL)			Zone size (mm)		
S	I	R	S	I	R
≤2	4	≥8	≥19	15 - 18	≤14

S = susceptible, I = intermediate, R = resistant

Figure 34 shows the scattergram constructed from the broth dilution MIC results and disk diffusion test results from the preclinical and clinical isolates tested.

Figure 34

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Figure 4.2.2.1.4-2: Error rate-bounded analysis for *Enterobacteriaceae* (clinical indication organisms *E. coli*, *K. pneumoniae*, *K. oxytoca*, *E. cloacae*, and *C. freundii*) for isolates from m-mITT population of patients from clinical protocols and preclinical data

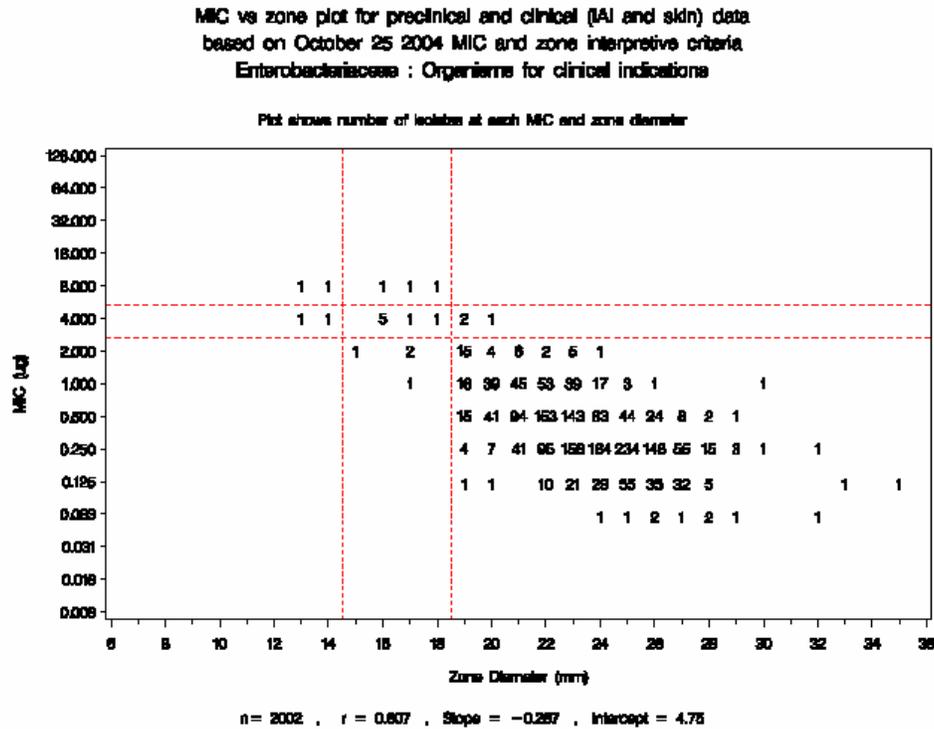


Table 4.2.2.1.4-2: Discrepancy Rates for tigecycline MIC and zone data for *Enterobacteriaceae* (clinical indication organisms *E. coli*, *K. pneumoniae*, *K. oxytoca*, *E. cloacae*, and *C. freundii*) for isolates from m-mITT population of patients from clinical protocols and preclinical data

MIC Range	Number of Isolates	Number of Discrepancies (Discrepancy Rate)		
		Very Major (%)	Major (%)	Minor (%)
$\geq(I+2)$	0	0	NA	0
(I+1) to (I-1)	53	0	0	11(20.8)
$\leq(I-2)$	1949	NA	0	1(0.1)
Total	2002	0	0	12(0.6)

Figure 35

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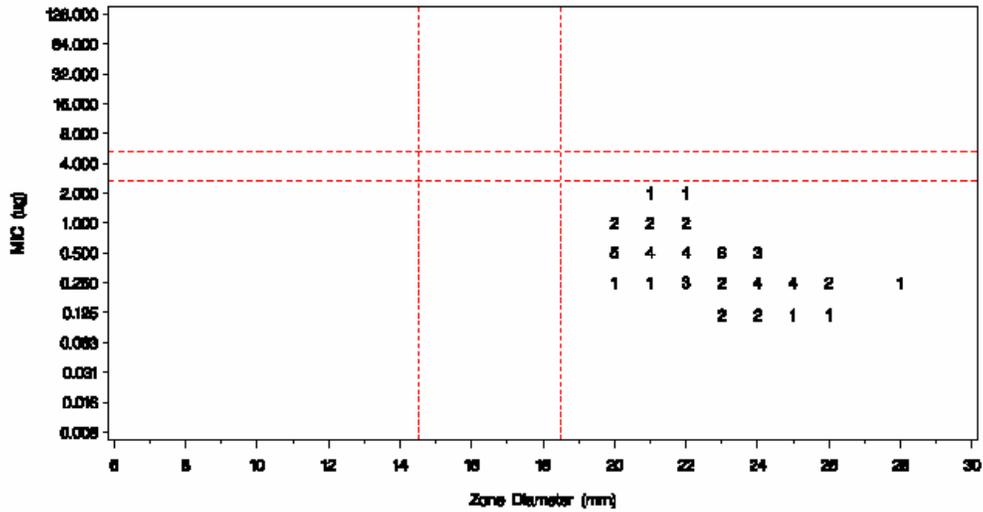
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Figure 4.2.2.1.4-2: Error Rate-Bounded Analysis for clinical isolates from skin protocols 300 and 305 (TGC treated ME population, all infections) for *Enterobacteriaceae*, organisms for clinical indications (*E. coli*, *K. pneumoniae*, *K. oxytoca*, *E. cloacae*, *C. freundii*)

MIC vs zone plot for data from skin protocols (300 and 305)
 based on proposed MIC and zone interpretive criteria
 Tigecycline 50 mg microbiologically evaluable patients
 Enterobacteriaceae : Organisms for clinical indications
 All Infections

Plot shows number of isolates at each MIC and zone diameter



n = 54 , r = 0.554 , Slope = -0.264 , Intercept = 5.061

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Figure 4.2.2.1.4-6: Error-rate bounded analysis for data from skin protocols (300 and 305) based on proposed MIC and zone interpretive criteria, Tigecycline microbiologically evaluable patients with microbiological response = eradication, Enterobacteriaceae: Organisms for clinical indications (*E. coli*, *K. pneumoniae*, *K. oxytoca*, *E. cloacae*, *C. freundii*) All infections

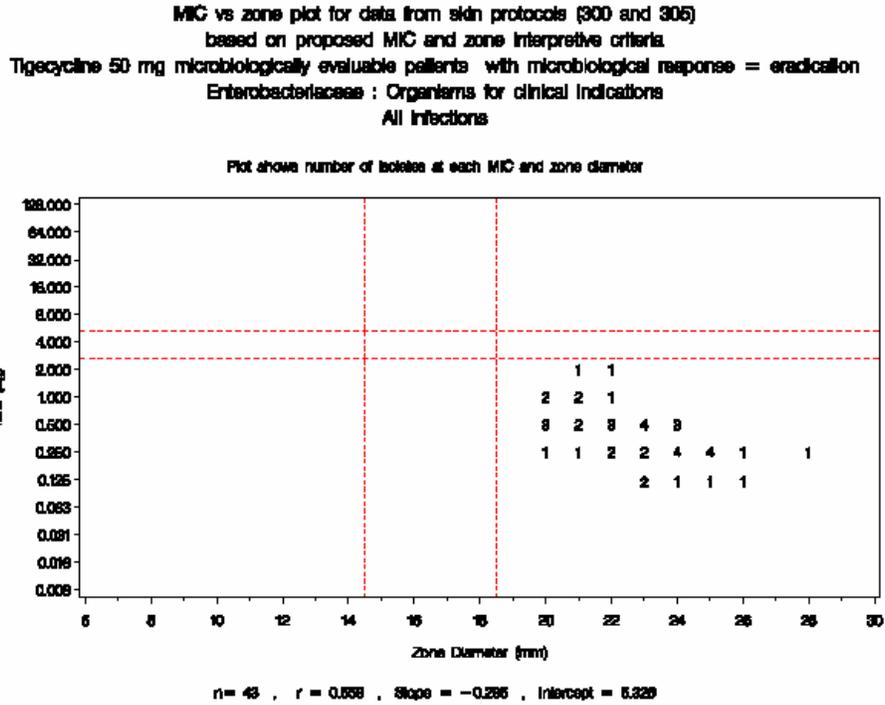


Figure 36

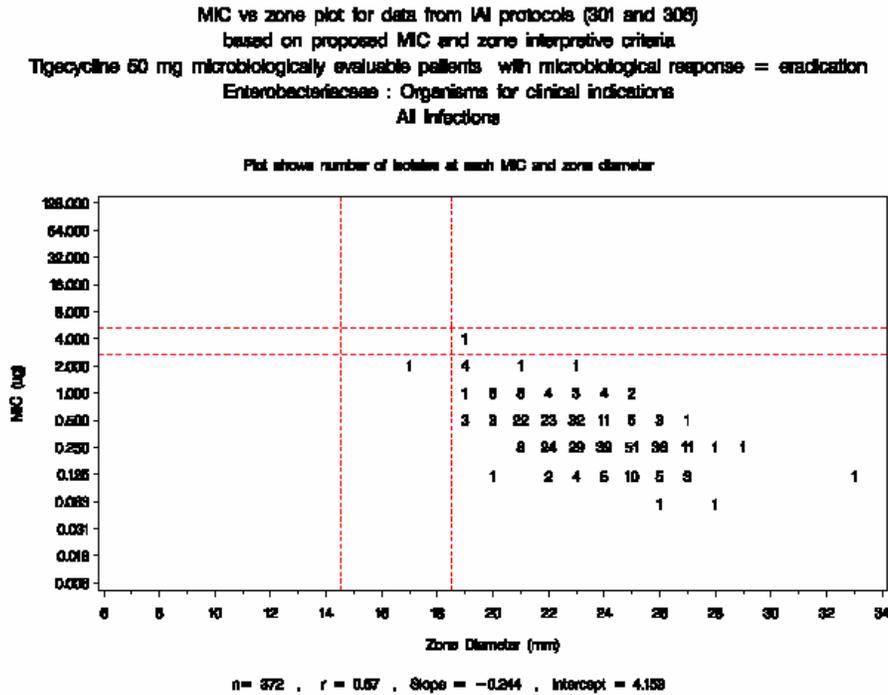
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Figure 4.2.2.2.4-6: Error rate-bounded analysis for data from IAI protocols (301 and 306) based on proposed MIC and zone interpretive criteria, Tigecycline microbiologically evaluable patients with microbiological response = eradication, Enterobacteriaceae : Organisms for clinical indications, (*E. coli*, *K. pneumoniae*, *K. oxytoca*, *E. cloacae*, *C. freundii*) All infections



CONCLUSION – ENTEROBACTERIACEAE

The Applicant provided clinical trial data for the following members of the *Enterobacteriaceae* family (*C. freundii*, *E. cloacae*, *E. coli*, *K. oxytoca* and *K. pneumoniae*). Based on the pharmacokinetics, pharmacodynamics, the clinical trial results for cIAI and cSSSI (see Tables 30, 31, and 33) preclinical and clinical in vitro susceptibility data the following in vitro susceptibility interpretive criteria are appropriate (Table 42). Because tigecycline has been shown to have reduced activity in vitro against *Morganella* spp., *Proteus* spp., and *Providencia* spp. a footnote will be added to the *Enterobacteriaceae* susceptibility interpretive table stating this.

Table 42. Tigecycline in vitro susceptibility test interpretive criteria for *Enterobacteriaceae*^a

MIC (µg/mL)			Zone size (mm)		
S	I	R	S	I	R
≤2	4	≥8	≥19	15 - 18	≤14

S = susceptible, I = intermediate, R = resistant

a. Tigecycline has reduced in vitro activity against *Morganella* spp, *Proteus* spp. and *Providencia* spp.

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Anaerobes

The Applicant is recommending that the in vitro agar dilution susceptibility test interpretive criteria for anaerobes be $\leq 4 \mu\text{g/ml}$ = susceptible, $(b)(4) \mu\text{g/mL}$ = intermediate, and $(b)(4) \mu\text{g/ml}$ = resistant.

Table 43 shows the overall susceptibility of anaerobic organisms to tigecycline. These data include isolates of *B. fragilis*, *B. thetaiotaomicron*, *B. vulgatus*, *B. uniformis*, *C. perfringens* and *P. micros*. As can be seen the two populations are similar in their cumulative susceptibility to tigecycline.

Table 43

Table 4.2.1.5-1: Tigecycline Susceptibility of Anaerobic Isolates From Preclinical and Clinical Tests (<i>B. fragilis</i>, <i>B. thetaiotaomicron</i>, <i>B. vulgatus</i>, <i>B. uniformis</i>, <i>C. perfringens</i> and <i>P. micros</i>.)										
Cumulative % of susceptible isolates at MIC	MIC ($\mu\text{g/mL}$)									
	0.06	0.12	0.25	0.5	1	2	4	8	16	32
Preclinical [1166]	0.1	0.9	3.3	19.3	48.5	79.5	88.2	94.9	99.1	100.0
Clinical [646]	13.2	22.6	39.0	66.1	84.7	92.0	94.3	97.2	100.0	
Total [1812]	4.7	8.6	16.0	36.0	61.4	83.9	90.3	95.7	99.4	100.0

Table 44 shows the cumulative susceptibility of isolates of *B. fragilis* isolated during clinical trials to tigecycline compared to the cumulative susceptibility of the *B. fragilis* isolates from pre-clinical in vitro susceptibility testing. As can be seen the two populations are similar in their cumulative susceptibility to tigecycline.

Table 44

Table 4.2.1.5-4: Tigecycline Susceptibility of <i>B. fragilis</i> Isolates From Preclinical and Clinical Tests										
Cumulative % of susceptible isolates at MIC	MIC ($\mu\text{g/mL}$)									
	0.06	0.12	0.25	0.5	1	2	4	8	16	32
Preclinical [624]		0.2	1.3	13.9	44.6	80.8	88.0	93.8	99.0	100.0
Clinical [311]	0.3	4.5	20.9	57.6	82.6	91.3	93.6	98.1	100.0	
Total [935]	0.1	1.6	7.8	28.4	57.2	84.3	89.8	95.2	99.4	100.0

CONCLUSION – ANAEROBES

The Applicant is recommending that the in vitro agar dilution susceptibility test interpretive criteria for anaerobes be $\leq 4 \mu\text{g/ml}$ = susceptible, $(b)(4) \mu\text{g/mL}$ = intermediate,

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and (b) (4) $\mu\text{g}/\text{ml}$ = resistant. Based on the preclinical and clinical tigecycline in vitro susceptibility test results, the pharmacokinetics of tigecycline and the bacteriological eradication and clinical outcome data primarily from the cIAI trials more appropriate in vitro agar susceptibility test interpretive criteria would be $\leq 4 \mu\text{g}/\text{ml}$ = susceptible, $8 \mu\text{g}/\text{mL}$ = intermediate and $\geq 16 \mu\text{g}/\text{ml}$ = resistant.

INDICATIONS AND USAGE SECTION OF PACKAGE INSERT

The Applicant is proposing to include the following organism under the proposed indications for tigecycline.

Complicated skin and skin structure infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible and –resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, and *Bacteroides fragilis*.

Complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.

SECOND LIST ORGANISMS

The criteria for organisms in the second list are: 1) they must be relevant to the indications, 2) There must be in vitro susceptibility data for at least 100 isolates of the organism, and 3) The MIC₉₀ for the organism must be within the achievable concentration of the antimicrobial using the approved dosage form, concentration, and administration. In addition, there may be certain microorganisms, such as community acquired methicillin-resistant *S. aureus* that are newly recognized as specific etiologies for a new disease entity. Such organisms will only be allowed in the “Indications and Usage” section of the label when there is sufficient clinical experience in treating that specific disease entity with a specific antimicrobial.

The Applicant is proposing the following organisms for the tigecycline package insert.

Aerobic gram-positive microorganisms

Enterococcus avium

Enterococcus casseliflavus

Enterococcus faecalis (vancomycin-resistant isolates)

Enterococcus faecium (vancomycin-susceptible and –resistant isolates)

Enterococcus gallinarium

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Listeria monocytogenes

(b) (4)

Staphylococcus epidermidis (Methicillin-susceptible and –resistant isolates)

Staphylococcus haemolyticus

(b) (4)

Aerobic gram-negative microorganisms

Acinetobacter baumannii

Aeromonas hydrophila

Citrobacter koseri

Enterobacter aerogenes

(b) (4)

Pasteurella multocida

(b) (4)

Serratia marcescens

(b) (4)

Stenotrophomonas maltophilia

Anaerobic microorganisms

Bacteroides distasonis

Bacteroides ovatus

(b) (4)

Peptostreptococcus spp.

Porphyromonas spp.

Prevotella spp.

Other microorganisms

Mycobacterium abscessus

Mycobacterium chelonae

Mycobacterium fortuitum

Organisms proposed for second list by the Agency

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In order for organisms to be included in the second list of the microbiology section of a package insert certain criteria must be met. These criteria are: 1) they must be relevant to the indications for which the drug is proposed, 2) the MIC₉₀ for the organisms must be within the therapeutic concentration of the antimicrobial that can be achieved with the proposed dosing regimen, The organisms being proposed for the second list of the tigecycline package insert by the Agency are provided below. The organisms that are not felt appropriate for the second list are indicated and the reason for their exclusion is provided

The organisms in the tigecycline package insert list would include the following:

Aerobic and facultative Gram-positive microorganisms

Enterococcus avium

Enterococcus casseliflavus

Enterococcus faecalis (vancomycin-resistant isolates)

Enterococcus faecium (vancomycin-susceptible and -resistant isolates)

Enterococcus gallinarum

Listeria monocytogenes

Staphylococcus epidermidis (methicillin-susceptible and -resistant isolates)

Aerobic and facultative Gram-negative microorganisms

Acinetobacter baumannii

Aeromonas hydrophila

Citrobacter koseri

Enterobacter aerogenes

Pasteurella multocida

Serratia marcescens

Stenotrophomonas maltophilia

Anaerobic microorganisms

Bacteroides distasonis

Bacteroides ovatus

Peptostreptococcus spp.

Porphyromonas spp.

Prevotella spp.

Other microorganisms

Mycobacterium abscessus

Mycobacterium chelonae

Mycobacterium fortuitum

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From a microbiology perspective the following organisms would not appear in the second list for the reasons stated.

(b) (4)

(b) (4)

(b) (4)

1. Because these organisms have recently been recognized as being associated with severe community-acquired skin infections and pneumonia and the disease is not well understood or the treatment for such infections clearly defined these organisms can only be included in the package insert after clinical studies have demonstrated that the antimicrobial, in this case tigecycline, can effectively treat the infection.

2. The following organisms will not be included in the second list because there is not sufficient clinical experience treating these infections with tigecycline or other antimicrobials. These organisms also represent a special set of bacteria that contain

(b) (4)

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(b) (4)

(b) (4)

(b) (4)

3. This organism is not relevant to the indications being sought.
4. While these organisms are members of the (b) (4) they are the cause of specific gastrointestinal illness and very rarely associated with cIAI.
5. This organism is not associated with cIAI. (b) (4)
(b) (4) Clinical studies are required to show that an antimicrobial can effectively treat the infection caused by this organism.
6. Tigecycline in vitro susceptibility data on less than 100 isolates provided by Applicant

10 Pages of Draft Labeling Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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HFD-520

CONCURRENCE ONLY

Lillian Gavrilovich, M.D.
Deputy Director
HFD-520
Finalized 14 Jun 05

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this page is the manifestation of the electronic signature.**

/s/

Frederic Marsik
6/15/05 04:15:26 PM
MICROBIOLOGIST

Lillian Gavrilovich
6/15/05 04:31:31 PM
MEDICAL OFFICER

Product Quality Microbiology Review

Review for HFD-520

23 MARCH 2005

NDA: 21-821

Drug Product Name

Proprietary: Tygacil

Non-proprietary: tigecycline

Drug Product Priority Classification: P

Review Number: 1

Subject of this Review

Submission Date: 15 December 2004

Receipt Date: 15 December 2004

Consult Date: 27 December 2004

Date Assigned for Review: 3 January 2005

Submission History (for amendments only)

Date(s) of Previous Submission(s): N/A

Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor

Name: Wyeth Pharmaceuticals Inc

Address: PO Box 8299, Philadelphia, PA 19101-8299

Representative: Randall B. Brenner

Telephone: 484-865-3792

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommend Approval with Comments for the Applicant

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** New NDA
 2. **SUBMISSION PROVIDES FOR:** Parenteral Anti-infective product
 3. **MANUFACTURING SITE:** Wyeth Parenterals Inc.
65th Infantry Avenue, Kilometer 9.7
Carolina, Puerto Rico 00987
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Lyophilized Powder for intravenous infusion in a 5 mL glass vial, 50 mg/vial
 5. **METHOD(S) OF STERILIZATION:** (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** Antimicrobial
- B. **SUPPORTING/RELATED DOCUMENTS:** N/A
- C. **REMARKS:** This was an eCTD submission

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Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – This submission is recommended for approval on the basis of product quality microbiology. Please see “List of Microbiology Comments” on page 11 of this review.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug product is (b) (4)
- B. Brief Description of Microbiology Deficiencies** – N/A
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
Bryan S. Riley, Ph.D. (Microbiology Reviewer)
David Hussong, Ph.D. (Microbiology Supervisor)
- C. CC Block**
N/A

8 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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

/s/

Bryan Riley
3/24/05 02:29:34 PM
MICROBIOLOGIST

David Hussong
3/24/05 04:14:35 PM
MICROBIOLOGIST