CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205645Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
Date review completed: 11-10-16

NDA 205645 Tigecycline for Injection

Date Company Submitted Document: 6-1-16 and 10-17-16
CDER Date Received: 6-1-16 and 10-17-16
Received for Review: 6-1-16 and 10-17-16
Reviewer: Kerian Grande Roche
Date Assigned: 6-1-16 and 10-17-16

NAME AND ADDRESS OF SPONSOR

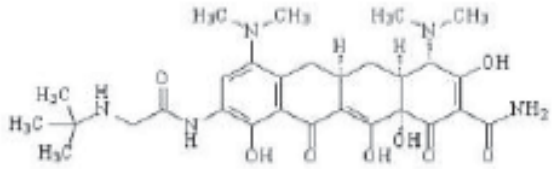
Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, IL 60047

CONTACT PERSON

Wanda Freeman-Sewell
Regulatory Specialist
(847) 550-2690

DRUG PRODUCT NAME

Proprietary Name: N/A
Established Name/Code Name(s): Tigecycline for Injection
Chemical Name: (4*S*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*- butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy 1,11-dioxo-2-naphthacenecarboxamide.
Chemical Formulae:



DRUG CATEGORY:

Antibiotic

PROPOSED INDICATION(S)

Tigecycline for injection is a tetracycline class antibacterial indicated in patients 18 years of age and older for:

- Complicated skin and skin structure infections
- Complicated intra-abdominal infections
- Community-acquired bacterial pneumonia

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

Dosage Form: lyophilized powder for reconstitution

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
Date review completed: 11-10-16

NDA 205645 Tigecycline for Injection
Route of Administration: Intravenous

Dosage: Initial dose of 100 mg, followed by 50 mg every 12 hours administered intravenously over approximately 30 to 60 minutes.

Strength: 50 mg in a single-dose 10 mL vial

Duration of Treatment: The recommended duration of treatment with tigecycline for injection for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days. The recommended duration of treatment with tigecycline for injection for community-acquired bacterial pneumonia is 7 to 14 days.

DISPENSED:
Rx

RELATED DOCUMENTS:
NDA 21821 Tycagil

REMARKS
The company submitted a 505 (b)(2) NDA for tigecycline for injection, 50 mg/vial on July 31, 2013. The Agency replied with a complete response letter on May 30, 2014 that stated deficiencies related to product quality. The company's complete response amendment was reviewed by clinical microbiology on 10-30-15. On 6-1-16 a class 2 resubmission was submitted by the Applicant with a quality information amendment and a request for final approval. No new clinical microbiology information was submitted. On 10-17-16 updates to the package insert were proposed by the Applicant. This review contains updates to the microbiology and references subsections of the labeling. These updates are to incorporate recommendations stated in the most current Clinical and Laboratory Standards Institute (CLSI) documents, and also current FDA guidance, "Microbiology Data for Systemic Antibacterial Drugs-Development, Analysis and Presentation".

CONCLUSIONS AND RECOMMENDATIONS
From a clinical microbiology standpoint this application may be approved with the recommended labeling changes as indicated below (See also Agency's proposed labeling):

- Language has been updated in subsection Microbiology12.4 in accordance with the guidance documents named above.
- Table 5 should list the quality control strain as *Clostridium difficile* ATCC 700057.
- CLSI Reference in section 15 has been updated to the most current reference (2016).

Agency's Proposed Package Insert (Microbiology subsection 12.4 and References subsection 15.0 only are shown.

12.4 Microbiology

Mechanism of Action

Tigecycline inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. In general, tigecycline is considered bacteriostatic; however, tigecycline has demonstrated bactericidal activity against isolates of *S. pneumoniae* and *L. pneumophila*.

Resistance

To date there has been no cross-resistance observed between tigecycline and other antibacterials. Tigecycline is less affected by the two major tetracycline-resistance mechanisms, ribosomal protection and efflux. Additionally, tigecycline is not affected by resistance mechanisms such as beta-lactamases (including extended spectrum beta-lactamases), target-site modifications, macrolide efflux pumps or enzyme target changes (e.g. gyrase/topoisomerases). However, some ESBL-producing isolates may confer resistance to tigecycline via other resistance mechanisms. Tigecycline resistance in some bacteria (e.g. *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex) is associated with multi-drug resistant (MDR) efflux pumps.

Interaction with Other Antimicrobials

In vitro studies have not demonstrated antagonism between tigecycline and other commonly used antibacterials.

Antimicrobial Activity

Tigecycline has been shown to be active against most of the following bacteria, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

Gram-positive Bacteria

Enterococcus faecalis (vancomycin-susceptible isolates)

Staphylococcus aureus (methicillin-susceptible and -resistant isolates)

Streptococcus agalactiae

Streptococcus anginosus group (includes *S. anginosus, S. intermedius,* and *S. constellatus*)

Streptococcus pneumoniae (penicillin-susceptible isolates)

Streptococcus pyogenes

Gram-negative Bacteria

Citrobacter freundii

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Klebsiella oxytoca

Klebsiella pneumoniae

Legionella pneumophila

Anaerobic Bacteria

Bacteroides fragilis

Bacteroides thetaiotaomicron

Bacteroides uniformis

Bacteroides vulgatus

Clostridium perfringens

Peptostreptococcus micros

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for tigecycline against isolates of similar genus or organism group. However, the efficacy of tigecycline in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive Bacteria

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

Gram-negative Bacteria

*Acinetobacter baumannii**

Aeromonas hydrophila

Citrobacter koseri

Enterobacter aerogenes

Haemophilus influenzae (ampicillin-resistant)

Haemophilus parainfluenzae

Pasteurella multocida

Serratia marcescens

Stenotrophomonas maltophilia

Anaerobic Bacteria

Bacteroides distasonis

Bacteroides ovatus

Peptostreptococcus spp.

Porphyromonas spp.

Prevotella spp.

Other Bacteria

Mycobacterium abscessus

Mycobacterium fortuitum

*There have been reports of the development of tigecycline resistance in *Acinetobacter* infections seen during the course of standard treatment. Such resistance appears to be attributable to an MDR efflux pump mechanism. While monitoring for relapse of infection is important for all infected patients, more frequent monitoring in this case is suggested. If relapse is suspected, blood and other specimens should be obtained and cultured for the presence of bacteria. All bacterial isolates should be identified and tested for susceptibility to tigecycline and other appropriate antimicrobials.

Susceptibility Test Methods

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

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method (broth, and/or agar~~, or microdilution~~) [1,3,4]. For broth dilution tests for aerobic organisms, MICs must be determined in testing medium that is fresh (< 12h old). The MIC values should be interpreted according to the criteria provided in Table 4.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method [2,4]. This procedure uses paper disks impregnated with 15 mcg tigecycline to test the susceptibility of bacteria to tigecycline. The disc diffusion breakpoints are noted in Table 4.

Anaerobic Techniques:

For anaerobic bacteria, the ~~Anaerobic~~ susceptibility to~~esting with~~ tigecycline can ~~should~~ be determined~~done~~ by a standardized test method ~~the agar dilution method~~ [3,4] ~~since quality control parameters for broth dilution are not established~~. The MIC values should be interpreted according to the criteria provided in Table 4.

Table 4. Susceptibility Test Result Interpretive Criteria for Tigecycline

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 0.5[a]	-	-	≥ 19	-	-
Streptococcus spp. other than *S. pneumoniae*	≤ 0.25[a]	-	-	≥ 19	-	-
Streptococcus pneumoniae	≤ 0.06[a]	-	-	≥ 19	-	-
Enterococcus faecalis (vancomycin-susceptible isolates)	≤ 0.25[a]	-	-	≥ 19	-	-
Enterobacteriaceae[b]	≤ 2	4	≥ 8	≥ 19	15 to 18	≤ 14
Haemophilus influenzae	≤ 0.25[a]	-	-	≥ 19	-	-
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 reference laboratory for further testing.
[b] Tigecycline has decreased *in vitro* activity against *Morganella* spp., *Proteus* spp. and *Providencia* spp.
[c] Agar dilution

A report of "*Susceptible*" (*S*) indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of "*Intermediate*" (*I*) indicates that the result should be considered equivocal~~,~~ and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of

drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "*Resistant*" (*R*) indicates that the antimicrobial drug is not likely to inhibit the growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the infection site; other therapy should be selected.

Quality Control:

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test [1,2,3,4]. Standard tigecycline powder should provide the ~~following~~ range of MIC values noted in Table 5. For the diffusion technique using the 15 mcg tigecycline disk, the criteria provided in Table 5 should be achieved.

Table 5. Acceptable Quality Control Ranges for Tigecycline

QC Strain	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
Staphylococcus aureus ATCC 25923	Not Applicable	20 to 25
Staphylococcus aureus ATCC 29213	0.03 to 0.25	Not Applicable
Escherichia coli ATCC 25922	0.03 to 0.25	20 to 27
Enterococcus faecalis ATCC 29212	0.03 to 0.12	Not Applicable
Streptococcus pneumoniae ATCC 49619	0.015 to 0.12	23 to 29
Haemophilus influenzae ATCC 49247	0.06 to 0.5	23 to 31
Neisseria gonorrhoeae ATCC 49226	Not Applicable	30 to 40
Bacteroides fragilis[a] ATCC 25285	0.12 to 1	Not Applicable
Bacteroides thetaiotaomicron[a] ATCC 29741	0.5 to 2	Not Applicable
Eggerthella lenta[a] ATCC 43055	0.06 to 0.5	Not Applicable
Clostridium difficile[a] ATCC 700057	0.125 to 1	Not Applicable
Pseudomonas aeruginosa[b] ATCC 27853	Not Applicable	9 to 13

ATCC = American Type Culture Collection
[a] Agar dilution
[b] *Pseudomonas aeruginosa* is included for quality control purpose only

15. REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Tenth Edition*. CLSI document M07-A10, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Twelfth Edition.* CLSI document M02-A12, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
3. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – Eighth Edition*. CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087, USA, 2012.
4. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-sixth Edition*. CLSI Supplement M100S. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2016.

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Clinical Microbiology Reviewer

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Acting Clinical Microbiology Team Leader
DAIP/OAP/OND/CDER
November 16, 2016

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

/s/

KERIAN K GRANDE ROCHE
11/16/2016

TAMARA V FELDBLYUM
11/16/2016

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
Date review completed: 10-30-15

NDA 205645 Tigecycline for Injection

Date Company Submitted Document: 5-29-15
Received for Review: 5-29-15
Date Assigned: 5-29-15

CDER Date Received: 5-29-15
Reviewer: Kerian Grande Roche

NAME AND ADDRESS OF SPONSOR

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CONTACT PERSON

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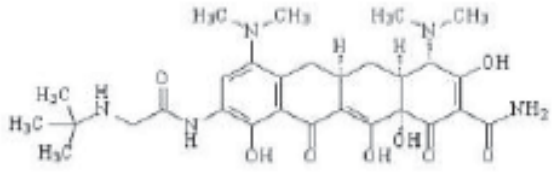
DRUG PRODUCT NAME

Proprietary Name: N/A
Established Name/Code Name(s): Tigecycline for Injection
Chemical Name: (4*S*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*- butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy 1,11-dioxo-2-naphthacenecarboxamide.
Chemical Formulae:



DRUG CATEGORY:

Antibiotic

PROPOSED INDICATION(S)

Tigecycline for injection is a tetracycline class antibacterial indicated in patients 18 years of age and older for:

- Complicated skin and skin structure infections
- Complicated intra-abdominal infections
- Community-acquired bacterial pneumonia

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

Dosage Form: lyophilized powder for reconstitution
Route of Administration: Intravenous

NDA 205645 Tigecycline for Injection

Dosage: Initial dose of 100 mg, followed by 50 mg every 12 hours administered intravenously over approximately 30 to 60 minutes.

Strength: 50 mg in a single-dose 10 mL vial
Duration of Treatment: The recommended duration of treatment with tigecycline for injection for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days. The recommended duration of treatment with tigecycline for injection for community-acquired bacterial pneumonia is 7 to 14 days.

DISPENSED:
Rx

RELATED DOCUMENTS:
NDA 21821 Tycagil

REMARKS
The company submitted a 505 (b)(2) NDA for tigecycline for injection, 50 mg/vial on July 31, 2013. The Agency replied with a complete response letter on May 30, 2014 that stated deficiencies related to product quality. This submission is the company's complete response amendment.

CONCLUSIONS AND RECOMMENDATIONS
From a clinical Microbiology standpoint this application may be approved with the recommended labeling changes as indicated below (See also Agency's proposed labeling):

- Language has been updated in subsection Microbiology12.4 in accordance with the Agency's current thinking, to remove promotional language, and to remove information that does not typically appear in this subsection.
- The abbreviation "grp." was changed to the word "group" since this is not a widely accepted abbreviation.
- In the Quality Control section, a footnote was added to *P. aeruginosa* to explain that this organism is only listed for quality control purposes, and is intrinsically resistant to tigecycline.
- References in section 15 have been updated to the most current references.

Agency's Proposed Package Insert (Microbiology subsection 12.4 and References subsection 15.0 only are shown. Edits are made to the Applicant's proposed labeling)

12.4 Microbiology

Mechanism of Action

Tigecycline~~,~~ (b) (4) ~~,~~ inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. (b) (4) In general, tigecycline is considered bacteriostatic; however, tigecycline has demonstrated bactericidal activity against isolates of *S. pneumoniae* and *L. pneumophila*.

(b) (4) Resistance

To date there has been no cross-resistance observed between tigecycline and other antibacterials. ~~Tigecycline is~~ (b) (4) ~~affected by the two major tetracycline resistance mechanisms, ribosomal protection and efflux. Additionally, tigecycline is not affected by resistance mechanisms such as beta-lactamases (including extended spectrum beta-lactamases), target-site modifications, macrolide efflux pumps or enzyme target changes (e.g. gyrase/topoisomerases).~~ Tigecycline resistance in some bacteria (e.g. *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex) is associated with multi-drug resistant (MDR) efflux pumps.

Interaction with Other Antimicrobials

In vitro studies have not demonstrated antagonism between tigecycline and other commonly used antibacterials.

Antimicrobial Activity

Tigecycline has been shown to be active against most of the following bacteria, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

(b) (4)-Gram-positive Bacteria

Enterococcus faecalis (vancomycin-susceptible isolates)

Staphylococcus aureus (methicillin-susceptible and -resistant isolates)

Streptococcus agalactiae

Streptococcus anginosus group (includes *S. anginosus, S. intermedius,* and *S. constellatus*)

Streptococcus pneumoniae (penicillin-susceptible isolates)

Streptococcus pyogenes

(b) (4) Gram-negative Bacteria

Citrobacter freundii

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae (b) (4)

Klebsiella oxytoca

Klebsiella pneumoniae

Legionella pneumophila

Anaerobic Bacteria

Bacteroides fragilis

Bacteroides thetaiotaomicron

Bacteroides uniformis

Bacteroides vulgatus

Clostridium perfringens

Peptostreptococcus micros

~~At least 90% of the following bacteria exhibit *in vitro* minimum inhibitory concentrations (MICs)~~ [redacted] ~~However,~~ [redacted] ~~of tigecycline in treating clinical infections due to these bacteria~~ [redacted] ~~not been established in adequate and well-controlled clinical trials.~~

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for tigecycline against isolates of similar genus or organism group. However, the efficacy of tigecycline in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

[redacted] Gram-positive Bacteria

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

[redacted] Gram-negative Bacteria

*Acinetobacter baumannii**

Aeromonas hydrophila

Citrobacter koseri

Enterobacter aerogenes

Haemophilus influenzae (ampicillin-resistant)

Haemophilus parainfluenzae

Pasteurella multocida

Serratia marcescens

Stenotrophomonas maltophilia

Anaerobic Bacteria

Bacteroides distasonis

Bacteroides ovatus

Peptostreptococcus spp.

Porphyromonas spp.

Prevotella spp.

Other Bacteria

Mycobacterium abscessus

Mycobacterium fortuitum

*There have been reports of the development of tigecycline resistance in *Acinetobacter* infections seen during the course of standard treatment. Such resistance appears to be attributable to an MDR efflux pump mechanism. While monitoring for relapse of infection is important for all infected patients, more frequent monitoring in this case is suggested. If relapse is suspected, blood and other specimens should be obtained and cultured for the presence of bacteria. All bacterial isolates should be identified and tested for susceptibility to tigecycline and other appropriate antimicrobials.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting (b) (4) an antibacterial (b) (4) drug for treatment.

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized (b) (4) test method (broth, and/or agar, or microdilution) [1,3,4] (b) (4) For broth dilution tests for aerobic organisms, MICs must be determined in testing medium that is fresh (< 12h old). The MIC values should be interpreted according to the criteria provided in Table 4.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method. [2,4] (b) (4) (b) (4) This procedure uses paper disks impregnated with 15 mcg tigecycline to test the susceptibility of bacteria to tigecycline. (b) (4) The disc diffusion breakpoints are noted in Table 4.

Anaerobic Techniques:

Anaerobic susceptibility testing with tigecycline should be done by the agar dilution method[3,4] since quality control parameters for broth-dilution are not established.

Table 4. Susceptibility Test Result Interpretive Criteria for Tigecycline

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 0.5[a]	-	-	≥ 19	-	-
Streptococcus spp. other than *S. pneumoniae*	≤ 0.25[a]	-	-	≥ 19	-	-
Streptococcus pneumoniae	≤ 0.06[a]	-	-	≥ 19	-	-
Enterococcus faecalis (vancomycin-susceptible isolates)	≤ 0.25[a]	-	-	≥ 19	-	-
Enterobacteriaceae[b]	≤ 2	4	≥ 8	≥ 19	15 to 18	≤ 14
Haemophilus influenzae	≤ 0.25[a]	-	-	≥ 19	-	-
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 reference laboratory for further testing.
[b] Tigecycline has decreased *in vitro* activity against *Morganella* spp., *Proteus* spp. and *Providencia* spp.
[c] Agar dilution

A report of "*Susceptible*" *(S)* indicates that the (b) (4) antimicrobial drug is likely to (b) (4)-inhibit (b) (4) growth of the pathogen if the antimicrobial drug (b) (4) reaches the concentration (b) (4) usually achievable at the site of infection. A report of "*Intermediate*" *(I)* indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "*Resistant*" *(R)* indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen (b) (4) if the antimicrobial (b) (4) drug reaches the concentration (b) (4) usually achievable; other therapy should be selected.

Quality Control:

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. [redacted] [1,2,3,4] Standard tigecycline powder should provide the following range of MIC values [redacted] noted in Table 5. For the diffusion technique using the 15 mcg tigecycline disk, the criteria provided in Table 5 should be achieved.

Table 5. Acceptable Quality Control Ranges for [redacted] -Tigecycline

QC [redacted] -Strain	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
Staphylococcus aureus ATCC 25923	Not Applicable	20 to 25
Staphylococcus aureus ATCC 29213	0.03 to 0.25	Not Applicable
Escherichia coli ATCC 25922	0.03 to 0.25	20 to 27
Enterococcus faecalis ATCC 29212	0.03 to 0.12	Not Applicable
Streptococcus pneumoniae ATCC 49619	0.0[redacted]5 to 0.12	23 to 29
Haemophilus influenzae ATCC 49247	0.06 to 0.5	23 to 31
Neisseria gonorrhoeae ATCC 49226	Not Applicable	30 to 40
Bacteroides fragilis[a] ATCC 25285	0.12 to 1	Not Applicable
Bacteroides thetaiotaomicron[a] ATCC 29741	0.5 to 2	Not Applicable
[redacted] *Eggerthella lenta*[a] ATCC 43055	0.06 to 0.5	Not Applicable
Clostridium difficile[a] ATCC 70057	0.125 to 1	Not Applicable
Pseudomonas aeruginosa[b] ATCC 27853	Not Applicable	9 to 13

ATCC = American Type Culture Collection
[a] Agar dilution
[b] *Pseudomonas aeruginosa* is included for quality control purpose only.

15 REFERENCES

~~1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard –* (b) (4)~~

~~2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard –* (b) (4)~~

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Tenth Edition*. CLSI document M07-A10, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Twelfth Edition.* CLSI document M02-A12, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
3. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – Eighth Edition*. CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087, USA, 2012.

~~4. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing;* (b) (4)~~

4. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fifth Informational Supplement*, CLSI document M100-S25, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
Date review completed: 10-30-15
NDA 205645 Tigecycline for Injection

Kerian Grande Roche, Ph.D.
Clinical Microbiology Reviewer

Kerry Snow, MS
Clinical Microbiology Supervisor
31 October 2015

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

/s/

KERIAN K GRANDE ROCHE
11/02/2015

KERRY SNOW
11/02/2015

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
Date review completed: 4-24-14
NDA 205645 Tigecycline for Injection

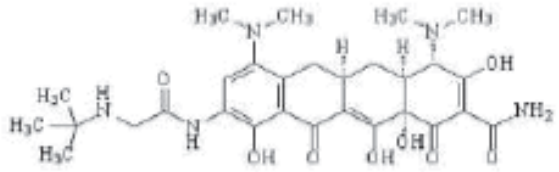
Date Company Submitted Document: 7-21-13
Received for Review: 8-1-13
Date Assigned: 8-1-13

CDER Date Received: 8-1-13
Reviewer: Kerian Grande Roche

NAME AND ADDRESS OF SPONSOR
Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, IL 60047

CONTACT PERSON
Wanda Freeman-Sewell
Regulatory Specialist
(847) 550-2690

DRUG PRODUCT NAME
Proprietary Name: N/A
Established Name/Code Name(s): Tigecycline for Injection
Chemical Name: (4*S*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*- butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy 1,11-dioxo-2-naphthacenecarboxamide.
Chemical Formulae:



DRUG CATEGORY:
Antibiotic

PROPOSED INDICATION(S)
Tigecycline for injection is a tetracycline class antibacterial indicated in patients 18 years of age and older for:

- Complicated skin and skin structure infections
- Complicated intra-abdominal infections
- Community-acquired bacterial pneumonia

PROPOSED DOSAGE FORM, DOSAGE, ROUTE OF ADMINISTRATION, STRENGTH AND DURATION OF TREATMENT
Dosage Form: lyophilized powder for reconstitution
Route of Administration: Intravenous

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
Date review completed: 4-24-14

NDA 205645 Tigecycline for Injection
Dosage: Initial dose of 100 mg, followed by 50 mg every 12 hours administered intravenously over approximately 30 to 60 minutes.

Strength: 50 mg in a single-dose 10 mL vial
Duration of Treatment: The recommended duration of treatment with tigecycline for injection for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days. The recommended duration of treatment with tigecycline for injection for community-acquired bacterial pneumonia is 7 to 14 days.

DISPENSED:
Rx

RELATED DOCUMENTS:
NDA 21821 Tycagil

REMARKS
This is a 505 (b)(2) NDA for tigecycline for injection, 50 mg/vial. The Applicant intends to rely on the Agency's finding of efficacy and safety for the reference listed drug (RLD), Tygacil (NDA 021821), to support this NDA. Both the Applicant's product and the RLD are administered intravenously. The Applicant's product contains the same active pharmaceutical ingredient (API) tigecycline in the same quantity as Tygacil. However, the Applicant's product contains a formulation change: L-arginine replaces lactose monohydrate as a (b) (4) This change is not expected to affect the pharmacokinetics or pharmacologic activity of tigecycline. The Applicant therefore intends to rely on the Agency's findings of safety and efficacy for the RLD Tygacil and the nonclinical information in the approved Tygacil labeling to support approval of its product.

CONCLUSIONS AND RECOMMENDATIONS
From a clinical Microbiology standpoint this application may be approved with the recommended labeling changes as indicated below (See also Agency's proposed labeling):

- Replace the word grp. with the word group as it applies to *Streptococcus anginosus* group, throughout the label. This includes where it appears in the indications and usage section, microbiology section 12.4, and Tables 7 and 9.
- Microbiology section 12.4: remove the word "(b) (4)" which precedes the words "Gram-positive" and "Gram-negative" in the lists of organisms.
- Under "Anaerobic Techniques", the section should be updated because quality control parameters have now been established for broth-dilution. Also, indicate that the media must not be older than 12 hours.
- Table 4 should be in alphabetical order.
- Table 5: *P. aeruginosa* ATCC 27853 has been added as a quality control organism, and both agar and microbroth dilution values have been added for the applicable organisms.
- References in section 15 have been updated to the most current references.

Applicant's Proposed Labeling (only sections 12.4 Microbiology and 15 References are shown)

12.4 Microbiology

Mechanism of Action

Tigecycline, (b) (4), inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. (b) (4) In general, tigecycline is considered bacteriostatic; however, tigecycline has demonstrated bactericidal activity against isolates of *S. pneumoniae* and *L. pneumophila*.

(b) (4) Resistance

To date there has been no cross-resistance observed between tigecycline and other antibacterials. Tigecycline is (b) (4) affected by the two major tetracycline-resistance mechanisms, ribosomal protection and efflux. Additionally, tigecycline is not affected by resistance mechanisms such as beta-lactamases (including extended spectrum beta-lactamases), target-site modifications, macrolide efflux pumps or enzyme target changes (e.g. gyrase/topoisomerases). Tigecycline resistance in some bacteria (e.g. *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex) is associated with multi-drug resistant (MDR) efflux pumps.

Interaction with Other Antimicrobials

In vitro studies have not demonstrated antagonism between tigecycline and other commonly used antibacterials.

Tigecycline has been shown to be active against most of the following bacteria, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

(b) (4) Gram-positive bacteria

Enterococcus faecalis (vancomycin-susceptible isolates)

Staphylococcus aureus (methicillin-susceptible and -resistant isolates)

Streptococcus agalactiae

Streptococcus anginosus grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*)

Streptococcus pneumoniae (penicillin-susceptible isolates)

Streptococcus pyogenes

(b) (4) Gram-negative bacteria

Citrobacter freundii

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae (b) (4)

Klebsiella oxytoca

Klebsiella pneumoniae

Legionella pneumophila

Anaerobic bacteria

Bacteroides fragilis

Bacteroides thetaiotaomicron

Bacteroides uniformis

Bacteroides vulgatus

Clostridium perfringens

Peptostreptococcus micros

At least 90% of the following bacteria exhibit *in vitro* minimum inhibitory concentrations (MICs) (b) (4) (b) (4) However, (b) (4) of tigecycline in treating clinical

infections due to these bacteria (b) (4) not been established in adequate and well-controlled clinical trials.

(b) (4) Gram-positive bacteria

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

(b) (4) Gram-negative bacteria

*Acinetobacter baumannii**

Aeromonas hydrophila

Citrobacter koseri

Enterobacter aerogenes

Haemophilus influenzae (ampicillin-resistant)

Haemophilus parainfluenzae

Pasteurella multocida

Serratia marcescens

Stenotrophomonas maltophilia

Anaerobic bacteria

Bacteroides distasonis

Bacteroides ovatus

Peptostreptococcus spp.

Porphyromonas spp.

Prevotella spp.

Other bacteria

Mycobacterium abscessus

Mycobacterium fortuitum

*There have been reports of the development of tigecycline resistance in *Acinetobacter* infections seen during the course of standard treatment. Such resistance appears to be attributable to an MDR efflux pump mechanism. While monitoring for relapse of infection is important for all infected patients, more frequent monitoring in this case is suggested. If relapse is suspected, blood and other specimens should be obtained and cultured for the presence of bacteria. All bacterial isolates should be identified and tested for susceptibility to tigecycline and other appropriate antimicrobials.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting (b) (4)

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized (b) (4) (broth, agar, or microdilution) [1, 3, 4] (b) (4) For broth dilution tests for aerobic organisms, MICs must be determined in testing medium that is fresh (< 12h old). The MIC values should be interpreted according to the criteria provided in Table 4.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. (b) (4) (b) (4) This procedure uses paper disks impregnated with 15 mcg tigecycline to test the susceptibility of bacteria to tigecycline. (b) (4) in Table 4.

Anaerobic Techniques

Anaerobic susceptibility testing with tigecycline should be done by the agar dilution method[3] since quality control parameters for broth-dilution are not established.

Table 4. Susceptibility Test Result Interpretive Criteria for Tigecycline

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 0.5[a]	-	-	≥ 19	-	-
Streptococcus spp. other than *S. pneumoniae*	≤ 0.25[a]	-	-	≥ 19	-	-
Streptococcus pneumoniae	≤ 0.06[a]	-	-	≥ 19	-	-
Enterococcus faecalis (vancomycin-susceptible isolates)	≤ 0.25[a]	-	-	≥ 19	-	-
Enterobacteriaceae[b]	≤ 2	4	≥ 8	≥ 19	15 to 18	≤ 14
Haemophilus influenzae	≤ 0.25[a]	-	-	≥ 19	-	-
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 reference laboratory for further testing.
[b] Tigecycline has decreased *in vitro* activity against *Morganella* spp., *Proteus* spp. and *Providencia* spp.
[c] Agar dilution

A report of "Susceptible" indicates that the (b) (4) is likely to (b) (4) inhibit (b) (4) if the antimicrobial (b) (4) reaches the concentratio (b) (4) usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs,

the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the (b) (4) is not likely to (b) (4) inhibit (b) (4) if the antimicrobial (b) (4) reaches the concentration (b) (4) usually achievable; other therapy should be selected.

Quality Control

(b) (4) [1, 2, 3, 4] Standard tigecycline powder should provide the MIC values (b) (4) in Table 5. For the diffusion technique using the 15 mcg tigecycline disk the criteria provided in Table 5 should be achieved.

Table 5. Acceptable Quality Control Ranges for (b) (4)

QC (b) (4)	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
Staphylococcus aureus ATCC 25923	Not Applicable	20 to 25
Staphylococcus aureus ATCC 29213	0.03 to 0.25	Not Applicable
Escherichia coli ATCC 25922	0.03 to 0.25	20 to 27
Enterococcus faecalis ATCC 29212	0.03 to 0.12	Not Applicable
Streptococcus pneumoniae ATCC 49619	(b) (4) to 0.12	23 to 29
Haemophilus influenzae ATCC 49247	0.06 to 0.5	23 to 31
Bacteroides fragilis[a] ATCC 25285	0.12 to 1	Not Applicable
Bacteroides thetaiotaomicron[a] ATCC 29741	0.5 to 2	Not Applicable
(b) (4) ATCC 43055	0.06 to 0.5	Not Applicable
Clostridium difficile[a] ATCC 70057	(b) (4) to 1	Not Applicable

ATCC = American Type Culture Collection
[a] Agar dilution

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically – (b) (4)
2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests – (b) (4)
3. Clinical and Laboratory Standards Institute (CLSI). Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria – (b) (4)
4. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing – (b) (4)

Agency's Proposed Labeling (only sections 12.4 Microbiology and 15 References are shown, see also conclusions section of this review for recommended changes outside these sections).

12.4 Microbiology

Mechanism of Action

Tigecycline, (b) (4), inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. (b) (4)

In general, tigecycline is considered bacteriostatic; however, tigecycline has demonstrated bactericidal activity against isolates of *S. pneumoniae* and *L. pneumophila*.

(b) (4) Resistance

To date there has been no cross-resistance observed between tigecycline and other antibacterials. Tigecycline is (b) (4) affected by the two major tetracycline-resistance mechanisms, ribosomal protection and efflux. Additionally, tigecycline is not affected by resistance mechanisms such as beta-lactamases (including extended spectrum beta-lactamases), target-site modifications, macrolide efflux pumps or enzyme target changes (e.g. gyrase/topoisomerases). Tigecycline resistance in some bacteria (e.g. *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex) is associated with multi-drug resistant (MDR) efflux pumps.

Interaction with Other Antimicrobials

In vitro studies have not demonstrated antagonism between tigecycline and other commonly used antibacterials.

Tigecycline has been shown to be active against most of the following bacteria, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

Gram-positive bacteria
Enterococcus faecalis (vancomycin-susceptible isolates)
Staphylococcus aureus (methicillin-susceptible and -resistant isolates)
Streptococcus agalactiae
Streptococcus anginosus group (includes *S. anginosus, S. intermedius,* and *S. constellatus*)
Streptococcus pneumoniae (penicillin-susceptible isolates)
Streptococcus pyogenes

Gram-negative bacteria
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae (b) (4)
Klebsiella oxytoca
Klebsiella pneumoniae
Legionella pneumophila

Anaerobic bacteria
Bacteroides fragilis
Bacteroides thetaiotaomicron
Bacteroides uniformis
Bacteroides vulgatus
Clostridium perfringens
Peptostreptococcus micros

At least 90% of the following bacteria exhibit *in vitro* minimum inhibitory concentrations (MICs) (b) (4) However, (b) (4) of tigecycline in treating clinical infections due to these bacteria (b) (4) not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria

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

Gram-negative bacteria

*Acinetobacter baumannii**

Aeromonas hydrophila

Citrobacter koseri

Enterobacter aerogenes

Haemophilus influenzae (ampicillin-resistant)

Haemophilus parainfluenzae

Pasteurella multocida

Serratia marcescens

Stenotrophomonas maltophilia

Anaerobic bacteria

Bacteroides distasonis

Bacteroides ovatus

Peptostreptococcus spp.

Porphyromonas spp.

Prevotella spp.

Other bacteria

Mycobacterium abscessus

Mycobacterium fortuitum

*There have been reports of the development of tigecycline resistance in *Acinetobacter* infections seen during the course of standard treatment. Such resistance appears to be attributable to an MDR efflux pump mechanism. While monitoring for relapse of infection is important for all infected patients, more frequent monitoring in this case is suggested. If relapse is suspected, blood and other specimens should be obtained and cultured for the presence of bacteria. All bacterial isolates should be identified and tested for susceptibility to tigecycline and other appropriate antimicrobials.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting (b) (4)

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized (b) (4) (broth, agar, or microdilution) [1,3,4] (b) (4)

For broth dilution tests for aerobic organisms, MICs must be determined in testing medium that is fresh (< 12h old). The MIC values should be interpreted according to the criteria provided in Table 4.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. (b) (4) (b) (4). This procedure uses paper disks impregnated with 15 mcg tigecycline to test the susceptibility of bacteria to tigecycline. (b) (4) in Table 4.

Anaerobic Techniques

Anaerobic susceptibility testing with tigecycline (b) (4) be done by the agar dilution (b) (4) methods [3,4]. (b) (4)

Table 4. Susceptibility Test Result Interpretive Criteria for Tigecycline

(b) (4)

A report of "Susceptible" indicates that the (b) (4) is likely to (b) (4) inhibi (b) (4) if the antimicrobial (b) (4) reaches the concentration (b) (4) usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the (b) (4) is not likely to (b) (4) inhibit (b) (4) if the antimicrobial (b) (4) reaches the concentration (b) (4) usually achievable; other therapy should be selected.

Quality Control

(b) (4)

[1,2,3,4] Standard tigecycline powder should provide the MIC values (b) (4) in Table 5. For the diffusion technique using the 15 mcg tigecycline disk the criteria provided in Table 5 should be achieved.

Table 5. Acceptable Quality Control Ranges for (b) (4)

QC (b) (4)	**Minimum Inhibitory Concentrations (mcg/mL)**	**Disk Diffusion (zone diameters in mm)**
Pseudomonas aeruginosa ATCC 27853	Not Applicable	9-13
Staphylococcus aureus ATCC 25923	Not Applicable	20 to 25
Staphylococcus aureus ATCC 29213	0.03 to 0.25	Not Applicable
Escherichia coli ATCC 25922	0.03 to 0.25	20 to 27
Enterococcus faecalis ATCC 29212	0.03 to 0.12	Not Applicable
Streptococcus pneumoniae ATCC 49619	(b) (4) to 0.12	23 to 29
Haemophilus influenzae ATCC 49247	0.06 to 0.5	23 to 31
Bacteroides fragilis ATCC 25285	0.12 to 1[a] (b) (4)	Not Applicable
Bacteroides thetaiotaomicron ATCC 29741	0.5 to 2[a] (b) (4)	Not Applicable
(b) (4) ATCC 43055	0.06 to 0.5	Not Applicable
Clostridium difficile ATCC 70057	0.125 to 1[a] (b) (4)	Not Applicable

ATCC = American Type Culture Collection
[a] Agar dilution
(b) (4)

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard* – (b) (4)

2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard* – (b) (4)

3. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial*

Susceptibility Testing of Anaerobic Bacteria; Approved Standard -Eight Edition. CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania ,19087, USA, 2012.

4. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing;* (b) (4)

Kerian Grande Roche, Ph.D.
Clinical Microbiology Reviewer

Peter Coderre, Ph.D.
Acting Clinical Microbiology Team Leader
23 April 2014

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

/s/

KERIAN K GRANDE ROCHE
04/28/2014

PETER E CODERRE
04/28/2014

Product Quality Microbiology Review

January 24, 2014

NDA: 205645

Drug Product Name
Proprietary: RLD Tygagil® manufactured by Wyeth
Non-proprietary: Tigecycline for injection, 50 mg/vial

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
July 31, 2013	August 1, 2013	August 05, 2013	August 07, 2013

Submission History (for 2nd Reviews or higher) – N/A

Applicant/Sponsor
Name: Fresenius Kabi USA, LLC
Address: Three Corporate Drive, Lake Zurich, IL 60047
Representative: Wanda Freeman-Sewell, Regulatory Specialist
Telephone: 847-550-2690

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA

2. SUBMISSION PROVIDES FOR: A market clearance for Tigecycline for injection.

3. MANUFACTURING SITE: Fresenius Kabi, Grand Island, NY

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile lyophilized powder, 50 mg/vial for intravenous infusion.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Antibacterial agent indicated for the treatment of skin, intra-abdominal and community acquired infections.

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: New Drug Application NDA 205645 is submitted by Fresenius Kabi USA, LLC (FK USA) to seek marketing clearance for Tigecycline for Injection. With the exception of a change in (b) (4), the Reference Listed Drug, Tygacil® (Tigecycline) for Injection, manufactured by Wyeth Pharmaceuticals Inc., is identical to the subject drug product. This is an electronic submission.

filename: **N205645R1**

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommend Approval

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) manufactured starting with (b) (4)

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

. Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist, OPS/CDER

B. Endorsement Block _____
John W. Metcalfe, Ph.D., Sr. Review Microbiologist, OPS/CDER

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE – N/A

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product –FK USA's Tigecycline for Injection is designed to be chemically, therapeutically, and functionally equivalent to Tygacil®, the Reference Listed Drug (RLD).

- Drug product composition – Table 1 (copied from Section 3.2.P.1, Table 3.2.P.1-2), represents the revised composition of the drug product.

Table 1. Composition per Unit Dose - Drug Product [961110]

Strength	50 mg/vial		
Packaging Configuration	(b) (4) mL fill in a 10-mL vial		
Vial	10 mL (b) (4) Type I Glass vial		
Stopper	(b) (4) rubber stopper		
Seal	20 mm, Flip-off Aluminum crimp seal		
Drug Product Name	**Content (per vial)**	**Function**	**Quality of ingredient**
Tigecycline	50	(b) (4)	N/A
Arginine	82.6		USP
Hydrochloric acid	As needed	pH adjuster	NF
Sodium hydroxide	As needed	pH adjuster	NF
(b) (4)			NF
			USP

- Description of container closure system – Container Closure System components are 10 cc (b) (4) glass vial, (b) (4) mm (b) (4) stopper.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity – Container closure integrity is measured by (b) (4) evaluates a vial's seal integrity by measuring the (b) (4)

(b) (4)

ADEQUATE

REVIEWER COMMENT – The applicant meets the regulatory expectations for validating the process used to test integrity of the primary packaging system.

P.3 Manufacture

P.3.1 Manufacturers – Fresenius Kabi, Grand Island, NY

P.3.3 Description of the Manufacturing Process and Process Controls

The sponsor is seeking market clearance for tigecycline for injection which is similar to the RLD Tygacil® for injection, with a slight difference in that, the (b) (4) lactose monohydrate has been substituted with L-arginine as shown in Table 2 (copied from Table 2.3.P.-4, Section 2.3.P). The remaining formulation remains identical.

Table 2. Formulation Comparison Between RLD and FK USA

	Tygacil ®	Tigecycline for Injection	Function of Ingredients
Ingredients	**Amount**	**Amount**	
Tigecycline	50 mg/vial	50 mg/vial	(b) (4)
Lactose Monohydrate	100 mg/vial	N/A	
L-Arginine, USP	N/A	82.6 mg/vial	
Hydrochloric Acid, NF	As needed	As needed	pH adjuster
Sodium Hydroxide, NF	As needed	As needed	pH adjuster
(b) (4)			

(b) (4)

- Microbial Limits – N/A

P.8.3 Stability Data – See Review Section P.8.1

ADEQUATE

REVIEWER COMMENT – The applicant meets the regulatory expectations with regard to the approved stability program to support the newly formulated drug product's microbiological quality throughout its shelf life.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

ADEQUATE

REVIEWER COMMENT – The labeling for the subject drug product is not likely to change from microbiology product quality standpoint, as the subject drug product is merely a change in the type of excipient from the previously approved drug product.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

None

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

/s/

VINAYAK B PAWAR
01/27/2014

JOHN W METCALFE
01/27/2014
I concur.