TIGECYCLINE

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TYGACIL

50 mg Lyophilized Powder for Injection (IV Infusion)

1. PHARMACOLOGIC CATEGORY

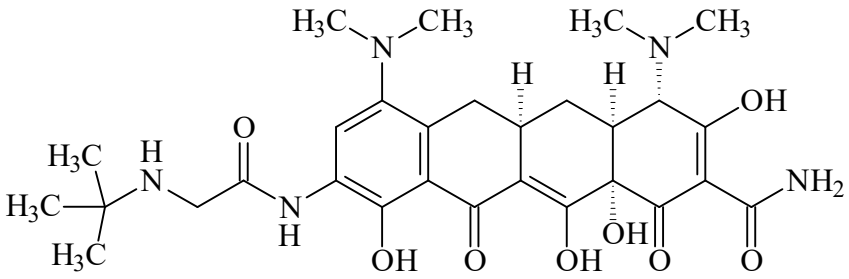
Antibacterial.

2. DESCRIPTION

Tigecycline (Tygacil) is a glycylcycline antibacterial for intravenous infusion. The chemical name of tigecycline (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.

The molecular formula is $C_{29}H_{39}N_5O_8$ and the molecular weight is 585.65.

The structural formula is represented below:



Tigecycline, in lyophilized powder form, is an orange lyophilized powder or cake. Constituted solution with 0.9% Sodium Chloride Solution appears to be clear, yellow to orange solution, essentially free of particulate matter.

3. FORMULATION/COMPOSITION

Each vial contains: 50 mg Tigecycline lyophilized powder, 100 mg Lactose monohydrate. The pH is adjusted with hydrochloric acid, and if necessary, sodium hydroxide. The product does not contain preservatives.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Tigecycline is indicated for treatment of the following infections in adults:

- Complicated skin and skin structure infections (cSSSI), including those with methicillin-resistant *Staphylococcus aureus* (MRSA).

Tigecycline is not indicated for the treatment of diabetic foot infections (DFI) (see Section **5.1 Pharmacodynamic properties**).

- Complicated intra-abdominal infections (cIAI).
- Community acquired pneumonia (CAP).

Tigecycline is not indicated for the treatment of hospital-acquired or ventilator-associated pneumonia (see Section **4.4 Special warnings and precautions for use**).

Pediatrics

Tigecycline is indicated in children from the age of eight years for treatment of the following infections only in situations where other alternative antibiotics are not suitable:

- Complicated skin and skin structure infections (cSSSI), including those with methicillin-resistant *Staphylococcus aureus* (MRSA)

  Tigecycline is not indicated for the treatment of diabetic foot infections (DFI). (see Section **5.1 Pharmacodynamic properties**)

- Complicated intra-abdominal infections (cIAI)

4.2 Dosage and method of administration

The recommended dosage regimen for adults for tigecycline is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous (IV) infusions of tigecycline should be administered over approximately 30 to 60 minutes every 12 hours.

The recommended duration of treatment with tigecycline for cSSSI or for cIAI is 5 to 14 days. The recommended duration of treatment with tigecycline for CAP is 7 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.

Use in patients with renal impairment

No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing hemodialysis (see Section **5.2 Pharmacokinetic properties**).

Use in patients with hepatic impairment

No dosage adjustment is necessary in patients (including pediatrics) with mild to moderate hepatic impairment (Child-Pugh A and Child-Pugh B). Based on the pharmacokinetic profile of tigecycline in patients with severe hepatic impairment (Child-Pugh C), the dose of tigecycline should be reduced by 50%. Adult dose should be altered

to 100 mg followed by 25 mg every 12 hours. Patients with severe hepatic impairment (Child-Pugh C) should be treated with caution and monitored for treatment response (see Section **5.2 Pharmacokinetic properties**).

Use in children

Tigecycline is only to be used to treat patients aged 8 years and older after consultation with a physician with appropriate experience in the management of infectious diseases. Tigecycline should not be used in children under 8 years of age due to the lack of data on safety and efficacy in this age group and because of teeth discoloration. (see Section **4.4 Special warnings and precautions for use**).

Pediatric patients aged 8 to 11 years should receive 1.2 mg/kg of tigecycline every 12 hours intravenously to a maximum dose of 50 mg of tigecycline every 12 hours.

Pediatric patients aged 12 to 17 years should receive 50 mg of tigecycline every 12 hours.

Intravenous (IV) infusions of tigecycline should be administered over approximately 30 to 60 minutes every 12 hours.

The proposed pediatric doses of tigecycline were chosen based on exposures observed in pharmacokinetic trials, which included small numbers of pediatric patients (see Section **5.2 Pharmacokinetic properties**).

Use in elderly

In a pooled analysis of 3900 subjects who received tigecycline in Phase 3 and 4 clinical studies, 1026 were 65 years and over. Of these, 419 were 75 years and over. No unexpected overall differences in safety were observed between these subjects and younger subjects. No dosage adjustment is necessary in elderly patients.

Race and gender

No dosage adjustment is necessary based on race or gender (see Section **5.2 Pharmacokinetic properties**).

Mode of administration

Intravenous infusion.

4.3 Contraindications

Tigecycline is contraindicated for use in patients who have known hypersensitivity to tigecycline.

4.4 Special warnings and precautions for use

An increase in all-cause mortality has been observed across Phase 3 and 4 clinical trials in tigecycline treated subjects versus comparator-treated subjects. In a pooled analysis of all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of subjects receiving tigecycline and 3.0% (110/3646) of subjects receiving comparator drugs resulting in an unadjusted risk difference of 0.9% (95% CI 0.1, 1.8). In a pooled analysis of these trials, based on a random effects model by trial weight, an adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1, 1.2) between tigecycline and comparator-treated subjects. The cause of this increase has not been established. This increase in all-cause mortality should be considered when selecting among treatment options (see Section **4.8 Undesirable effects**).

Anaphylactic reaction/anaphylactoid reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening.

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. Therefore, tigecycline should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics.

Results of studies in rats with tigecycline have shown bone discoloration. Tigecycline may be associated with permanent tooth discoloration in humans during tooth development.

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

Caution should be exercised when considering tigecycline monotherapy in patients with cIAI secondary to clinically apparent intestinal perforation. In Phase 3 and 4 cIAI studies (n=2775), 140/1382 tigecycline-treated subjects and 142/1393 comparator-treated subjects presented with intestinal perforations. Of these subjects, 8/140 subjects treated with tigecycline and 8/142 subjects treated with comparator developed sepsis/septic shock. The relationship of this outcome to treatment cannot be established.

Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline.

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia).

Pancreatitis acute, which can be fatal, has occurred (frequency: uncommon) in association with tigecycline treatment (see Section **4.8 Undesirable effects**). The diagnosis of pancreatitis acute should be considered in patients taking tigecycline who develop clinical symptoms, signs, or laboratory abnormalities suggestive of pancreatitis acute. Cases have been reported in patients without known risk factors for pancreatitis.

Patients usually improve after tigecycline discontinuation. Consideration should be given to the cessation of the treatment with tigecycline in patients suspected of having developed pancreatitis.

Monitoring of blood coagulation parameters, including blood fibrinogen, is recommended prior to treatment initiation with tigecycline and regularly while on treatment. (see Section **4.8 Undesirable effects**).

The safety and efficacy of tigecycline in patients with hospital acquired pneumonia (HAP) have not been established. In a study of subjects with HAP, subjects were randomized to receive tigecycline (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, subjects were allowed to receive specified adjunctive therapies. The sub-group of subjects with ventilator-associated pneumonia (VAP) who received tigecycline had lower cure rates (47.9% versus 70.1% for the clinically evaluable population) and greater mortality (25/131 [19.1%] versus 15/122 [12.3%]) than the comparator. Of those subjects with VAP and bacteremia at baseline, those who received tigecycline had greater mortality (9/18 [50.0%] versus 1/13 [7.7%]) than the comparator.

As with other antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

Pediatric population

Clinical experience in the use of tigecycline for the treatment of infections in pediatric patients aged 8 years and older is very limited (see Sections **4.8 Undesirable effects** and **5.1 Pharmacodynamic properties**). Consequently, use in children should be restricted to those clinical situations where no alternative antibacterial therapy is available.

Nausea and vomiting are very common adverse reactions in children and adolescents (see Section **4.8 Undesirable effects**). Attention should be paid to possible dehydration.

Abdominal pain is commonly reported in children as it is in adults. Abdominal pain may be indicative of pancreatitis. If pancreatitis develops, treatment with tigecycline should be discontinued.

Liver function tests, coagulation parameters, hematology parameters, amylase and lipase should be monitored prior to treatment initiation with tigecycline and regularly while on treatment.

Tigecycline should not be used in children under 8 years of age due to the lack of safety and efficacy data in this age group and because tigecycline may be associated with permanent teeth discoloration (see Sections **4.2 Dosage and method of administration** and **4.8 Undesirable effects**).

4.5 Interaction with other medicinal products and other forms of interaction

Tigecycline (100 mg followed by 50 mg every 12 hours) and digoxin (0.5 mg followed by 0.25 mg every 24 hours) were co-administered to healthy subjects in a drug interaction study. Tigecycline slightly decreased the C_{max} of digoxin by 13%, but did not affect the AUC or clearance of digoxin. This small change in C_{max} did not affect the steady-state pharmacodynamic effects of digoxin as measured by changes in ECG intervals. In addition, digoxin did not affect the pharmacokinetic profile of tigecycline. Therefore, no dosage adjustment is necessary when tigecycline is administered with digoxin.

Concomitant administration of tigecycline (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single dose) to healthy subjects resulted in a decrease in clearance of R-warfarin and S-warfarin by 40% and 23%, and an increase in AUC by 68% and 29%, respectively. Tigecycline did not significantly alter the effects of warfarin on increased international normalized ratio (INR). In addition, warfarin did not affect the pharmacokinetic profile of tigecycline. However, prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin.

In vitro studies in human liver microsomes indicate that tigecycline does not inhibit metabolism mediated by any of the following 6 cytochrome CYP450 isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. Therefore, tigecycline is not expected to alter the metabolism of drugs metabolized by these enzymes. In addition, because tigecycline is not extensively metabolized, clearance of tigecycline is not expected to be affected by drugs that inhibit or induce the activity of these CYP450 isoforms.

In vitro studies using Caco-2 cells indicate that tigecycline does not inhibit digoxin flux, suggesting that tigecycline is not a P-glycoprotein (P-gp) inhibitor. This *in vitro* information is consistent with the lack of effect of tigecycline on digoxin clearance noted in the *in vivo* drug interaction study described above.

Tigecycline is a substrate of P-gp based on an *in vitro* study using a cell line overexpressing P-gp. The potential contribution of P-gp-mediated transport to the *in vivo* disposition of tigecycline is not known. Co-administration of P-gp inhibitors (e.g., ketoconazole or cyclosporine) or P-gp inducers (e.g., rifampicin) could affect the pharmacokinetics of tigecycline.

Concurrent use of antibiotics with oral contraceptives may render oral contraceptives less effective.

Concomitant use of tigecycline and calcineurin inhibitors such as tacrolimus or cyclosporine may lead to an increase in serum trough concentrations of the calcineurin inhibitors. Therefore, serum concentrations of the calcineurin inhibitor should be monitored during treatment with tigecycline to avoid drug toxicity.

Interference with laboratory and other diagnostic tests
There are no reported drug-laboratory test interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy
Tigecycline may cause fetal harm when administered to a pregnant woman. Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. Decreased fetal weights in rats and rabbits (with associated delays in ossification) have been observed with tigecycline.

Tigecycline was not teratogenic in the rat or rabbit (see Section **5.3 Preclinical safety data**).

There are no adequate and well-controlled studies of tigecycline in pregnant women. Tigecycline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Tigecycline has not been studied for use during labor and delivery.

Lactation
It is not known whether this drug is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of tigecycline/metabolites in milk (see Section **5.3 Preclinical safety data**). Because many drugs are excreted in human milk, caution should be exercised when tigecycline is administered to a nursing woman (see Section **4.4 Dosage and method of administration**).

Fertility
The effects of tigecycline on fertility in humans have not been studied. Nonclinical studies conducted with tigecycline in rats do not indicate harmful effects with respect to fertility or reproductive performance (see Section **5.3 Preclinical safety data**).

4.7 Effects on ability to drive and use machines

Tigecycline can cause dizziness (see Section **4.8 Undesirable effects**), which may impair the ability to drive and/or operate machinery.

4.8 Undesirable effects

Expected frequency of adverse reactions is presented in CIOMS frequency categories:	
Very Common	≥10%
Common	≥1% and <10%
Uncommon	≥0.1% and <1%
Rare	≥0.01% and <0.1%
Very rare	<0.01%
Frequency not known	cannot be estimated from the available data

For patients who received tigecycline, the following adverse reactions were reported:

System Organ Class	**Adverse Reaction**
Blood and lymphatic system disorders	
Common	Activated partial thromboplastin time prolonged (aPTT), prothrombin time prolonged (PT), thrombocytopenia
Uncommon	International normalized ratio increased (INR)
Rare	Hypofibrinogenemia
Immune system disorders	
Frequency not known	Anaphylactic reaction/anaphylactoid reaction
Metabolism and nutrition disorders	
Common	Hypoproteinemia, hypoglycemia, decreased appetite
Nervous system disorders	
Common	Dizziness, headache
Vascular disorders	
Common	Phlebitis
Uncommon	Thrombophlebitis
Respiratory, thoracic and mediastinal disorders	
Common	Pneumonia

System Organ Class	Adverse Reaction
Gastrointestinal disorders	
Very common	Nausea, vomiting, diarrhea
Common	Abdominal pain, dyspepsia
Uncommon	Pancreatitis acute
Hepato-biliary disorders	
Common	Aspartate aminotransferase (AST) increased alanine aminotransferase (ALT) increased*, hyperbilirubinemia
Uncommon	Jaundice
Frequency not known	Cholestasis

*AST and ALT abnormalities in tigecycline-treated patients were reported more frequently in the post-therapy period than in those in comparator-treated patients, which occurred more often on therapy.

Skin and subcutaneous tissue disorders	
Common	Pruritus, rash
Frequency not known	Severe skin reactions, including Stevens-Johnson syndrome
General disorders and administration site conditions	
Common	Impaired healing, injection site reaction
Uncommon	Injection site inflammation, injection site pain, injection site edema, injection site phlebitis
Investigations	
Common	Amylase increased, blood urea increased (BUN)

In a pooled analysis of all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of subjects receiving tigecycline and 3.0% (110/3646) of subjects receiving comparator drugs. In a pooled analysis of these trials, the risk difference of all-cause mortality was 0.9% (95% CI 0.1, 1.8) between tigecycline and comparator-treated subjects. In a pooled analysis of these trials, based on a random effects model by trial weight, an adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1, 1.2) between tigecycline-treated and comparator-treated subjects. No significant differences were observed between tigecycline and comparators within each infection type (see Table 1). The cause of the imbalance has not been established. Generally, deaths were the result of worsening infection, or complications of infection or underlying co-morbidities.

Table 1. Subjects with Outcome of Death by Infection Type					
	-Tigecycline-		-Comparator-		Risk Difference*
Infection Type	n/N	%	n/N	%	% (95% CI)
cSSSI	12/834	1.4	6/813	0.7	0.7 (-0.5, 1.9)
cIAI	42/1382	3.0	31/1393	2.2	0.8 (-0.4, 2.1)
CAP	12/424	2.8	11/422	2.6	0.2 (-2.3, 2.7)
HAP	66/467	14.1	57/467	12.2	1.9 (-2.6, 6.4)
Non-VAP[a]	41/336	12.2	42/345	12.2	0.0 (-5.1, 5.2)
VAP[a]	25/131	19.1	15/122	12.3	6.8 (-2.9, 16.2)
RP	11/128	8.6	2/43	4.7	3.9 (-9.1, 11.6)
DFI	7/553	1.3	3/508	0.6	0.7 (-0.8, 2.2)
Overall Unadjusted	150/3788	4.0	110/3646	3.0	0.9 (0.1, 1.8)
Overall Adjusted	150/3788	4.0	110/3646	3.0	0.6 (0.1, 1.2)**

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI = Complicated skin and skin structure infections; HAP = hospital-acquired pneumonia; VAP = ventilator-associated pneumonia; RP = resistant pathogens; DFI = diabetic foot infections.

* The difference between the percentage of subjects who died in tigecycline and comparator treatment groups. The 95% CIs were calculated using the Wilson Score Method with continuity correction.
** Overall adjusted (random effects model by trial weight) risk difference estimate and 95% CI.
[a] These are subgroups of the HAP population.

Note: The trials include 300, 305, 900 (cSSSI), 301, 306, 315, 316, 400 (cIAI), 308 and 313 (CAP), 311 (HAP), 307 [Resistant gram-positive pathogen study in subjects with MRSA or Vancomycin-Resistant *Enterococcus* (VRE)], and 319 (DFI with and without osteomyelitis).

The most common treatment-emergent adverse reactions in subjects treated with tigecycline were nausea 29.9% (19.3% mild; 9.2% moderate; 1.4% severe) and vomiting 19.9% (12.1% mild; 6.8% moderate; 1.1% severe). In general, nausea or vomiting occurred early (Days 1-2).

Discontinuation from tigecycline was most frequently associated with nausea (1.6%) and vomiting (1.3%).

Pediatric population

Very limited safety data were available from two PK studies. (see Section **5.2 Pharmacokinetic properties**) No new or unexpected safety concerns were observed with tigecycline in these studies.

In an open-label, single ascending dose PK study, the safety of tigecycline was investigated in 25 children aged 8 to 16 years who recently recovered from infections. The adverse reaction profile of tigecycline in these 25 subjects was generally consistent with that in adults.

The safety of tigecycline was also investigated in an open-label, ascending multi-dose PK study in 58 children aged 8 to 11 years with cSSSI (n=15), cIAI (n=24) or community-acquired pneumonia (n=19). The adverse reaction profile of tigecycline in these 58 subjects was generally consistent with that in adults, with the exception of nausea (48.3%), vomiting (46.6%) and elevated lipase in serum (6.9%) which were seen at greater frequencies in children than in adults.

4.9 Overdose and treatment

No specific information is available on the treatment of overdose with tigecycline. Intravenous administration of tigecycline at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. In single-dose IV toxicity studies conducted with tigecycline in mice, the estimated median lethal dose (LD_{50}) was 124 mg/kg in males and 98 mg/kg in females. In rats, the estimated LD_{50} was 106 mg/kg for both sexes. Tigecycline is not removed in significant quantities by hemodialysis.

4.10 Abuse and dependence

Drug abuse and dependence have not been demonstrated and are unlikely.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Tigecycline, a glycylcycline antibiotic, 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. Tigecycline carries a glycylamido moiety attached to the 9-position of minocycline. The substitution pattern is not present in any naturally occurring or semisynthetic tetracycline and imparts certain microbiologic properties that transcend any known tetracycline-derivative *in vitro* or *in vivo* activity. In addition, tigecycline is able to overcome the two major tetracycline resistance mechanisms, ribosomal protection and efflux. Accordingly, tigecycline has demonstrated *in vitro* and *in vivo* activity against a broad spectrum of bacterial pathogens. There has been no cross resistance observed between tigecycline and other antibiotics. In *in vitro* studies, no antagonism has been observed between tigecycline and other commonly used antibiotics. In general, tigecycline is considered bacteriostatic. At 4 times the minimum inhibitory concentration (MIC), a 2-log reduction in colony counts was observed with tigecycline against *Enterococcus* spp., *Staphylococcus aureus*, and *Escherichia coli*. However, tigecycline has shown some bactericidal activity, and a 3-log reduction was observed against *Neisseria gonorrhoeae*. Tigecycline has also demonstrated bactericidal activity against common respiratory strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Legionella pneumophila*.

Susceptibility Test Methods

Dilution Techniques

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure based on dilution methods (broth, agar, or microdilution) or equivalent using standardized inoculum and concentrations of tigecycline. For broth dilution tests for aerobic organisms, MICs must be determined using testing medium that is fresh (<12 hours old). The MIC values should be interpreted according to the criteria provided in Table 2.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 µg tigecycline to test the susceptibility of microorganisms to tigecycline. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for tigecycline. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 µg tigecycline disk should be interpreted according to the criteria in Table 2.

Table 2. Susceptibility Test Result Interpretive Criteria for Tigecycline

	Minimum Inhibitory Concentrations (µg/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	≤0.12[a]	-	-	≥21	-	-
Enterococcus faecalis (vancomycin-susceptible isolates only)	≤0.25[a]	-	-	≥19	-	-
Enterobacteriaceae[b]	≤2	4	≥8	≥19	15-18	≤14
Haemophilus influenzae	≤1[a]	-	-	≥21	-	-
Moraxella catarrhalis	≤0.12[a]	-	-	≥27	-	-
Anaerobes[c]	≤4	8	≥16	n/a	n/a	n/a

S= Susceptible; I=Intermediate; R=Resistant.

[a] The current absence of resistant isolates precludes defining any results other than "Susceptible." Isolates yielding MIC results suggestive of "Non-susceptible" 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 pathogen is likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test

should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where 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 pathogen is not likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standard tigecycline powder should provide the MIC values provided in Table 3. For the diffusion technique using the 15 μg tigecycline disk, laboratories should use the criteria provided in Table 3 to test quality control strains.

Table 3. Acceptable Quality Control Ranges for Susceptibility Testing

QC organism	Minimum Inhibitory Concentrations (μg/mL)	Disk Diffusion (zone diameters in mm)
Staphylococcus aureus ATCC 25923	Not Applicable	20-25
Staphylococcus aureus ATCC 29213	0.03-0.25	Not Applicable
Escherichia coli ATCC 25922	0.03-0.25	20-27
Enterococcus faecalis ATCC 29212	0.03-0.12	Not Applicable
Pseudomonas aeruginosa ATCC 27853	Not Applicable	9-13
Streptococcus pneumoniae ATCC 49619	0.016-0.12	23-29
Haemophilus influenzae ATCC 49247	0.06-0.5	23-31
Neisseria gonorrhoeae ATCC 49226	Not Applicable	30-40
Bacteroides fragilis ATCC 25285	0.12-1	Not Applicable
Bacteroides thetaiotaomicron ATCC 29741	0.5-2	Not Applicable
Eubacterium lentum ATCC 43055	0.06-0.5	Not Applicable
Clostridium difficile ATCC 70057	0.12-1	Not Applicable

ATCC = American Type Culture Collection.

The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. The information below provides only approximate guidance on the probability as to whether the microorganism will be susceptible to tigecycline or not:

Susceptible

Gram-positive aerobes:

Enterococcus avium
Enterococcus casseliflavus
*Enterococcus faecalis****** (includes vancomycin-susceptible strains)
Enterococcus faecalis (includes vancomycin-resistant strains)
Enterococcus faecium (includes vancomycin-susceptible and -resistant strains)
Enterococcus gallinarum

Listeria monocytogenes
*Staphylococcus aureus** (includes methicillin-susceptible and -resistant strains, including isolates that bear molecular and virulence markers commonly associated with community acquired MRSA including the SCCmec type IV element and the pvl gene)
Staphylococcus epidermidis (includes methicillin-susceptible and -resistant strains)
Staphylococcus haemolyticus
*Streptococcus agalactiae**
*Streptococcus anginosus** (includes *S. anginosus*, *S. intermedius*, *S. constellatus*)
*Streptococcus pyogenes**
*Streptococcus pneumoniae** (penicillin-susceptible isolates)
Streptococcus pneumoniae (penicillin-resistant isolates)
Viridans group streptococci

Gram-negative aerobes:
Acinetobacter calcoaceticus/baumannii complex
Aeromonas hydrophila
*Citrobacter freundii**
Citrobacter koseri
Enterobacter aerogenes
*Enterobacter cloacae**
*Escherichia coli** (including extended spectrum beta lactamase-producing strains)
*Haemophilus influenzae**
Haemophilus parainfluenzae
*Klebsiella oxytoca**
*Klebsiella pneumoniae** (including extended spectrum beta lactamase-producing strains)
Klebsiella pneumoniae (including AmpC producing strains)
*Legionella pneumophila**
*Moraxella catarrhalis**
Neisseria gonorrhoeae
Neisseria meningitidis
Pasteurella multocida
Salmonella enterica ser. Enteritidis
Salmonella enterica ser. Paratyphi
Salmonella enterica ser. Typhi
Salmonella enterica ser. Typhimurium
Serratia marcescens
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Shigella sonnei
Stenotrophomonas maltophilia

Anaerobic bacteria:
*Bacteroides fragilis**
Bacteroides distasonis
Bacteroides ovatus

*Bacteroides thetaiotaomicron**
*Bacteroides uniformis**
*Bacteroides vulgatus**
Clostridium difficile
*Clostridium perfringens**
Peptostreptococcus spp.
*Peptostreptococcus micros**
Porphyromonas spp.
Prevotella spp.

Atypical bacteria:
*Chlamydia pneumoniae**
Mycobacterium abscessus
Mycobacterium chelonae
Mycobacterium fortuitum
*Mycoplasma pneumoniae**

*Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.

Resistant

Gram-negative aerobes:
Pseudomonas aeruginosa.

Anaerobic bacteria:
No naturally-occurring species have been found to be inherently resistant to tigecycline.

Resistance:
There has been no cross-resistance observed between tigecycline and other antibiotics.

Tigecycline is able to overcome the two major tetracycline resistance mechanisms, ribosomal protection and efflux.

In *in vitro* studies, no antagonism has been observed between tigecycline and any other commonly used antibiotic class.

Clinical Trial Data on Efficacy

Complicated Skin and Skin Structure Infections (cSSSI)

Tigecycline was evaluated in adults for the treatment of cSSSI in two randomized, double-blind, active-controlled, multinational, multicenter studies. These studies compared tigecycline (100 mg IV initial dose followed by 50 mg every 12 hours) with vancomycin (1 g IV every 12 hours)/aztreonam (2 g IV every 12 hours) for 5 to 14 days. Subjects with complicated deep soft-tissue infections, including wound infections and cellulitis (≥10 cm, requiring surgery/drainage or with complicated underlying disease), major abscesses, infected ulcers, and burns were enrolled in the studies. The primary

efficacy endpoint was the clinical response at the test of cure (TOC) visit in the co-primary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) subjects. See Table 4.

Table 4. Clinical Cure Rates from Two Pivotal Studies in cSSSI after 5 to 14 Days of Therapy

	Tigecycline[a] n/N (%)	Vancomycin/ Aztreonam[b] n/N (%)
CE	365/422 (86.5)	364/411 (88.6)
c-mITT	429/538 (79.7)	425/519 (81.9)

[a] 100 mg initially, followed by 50 mg every 12 hours.
[b] Vancomycin (1 g IV every 12 hours)/Aztreonam (2 g IV every 12 hours).

Clinical cure rates at TOC by pathogen in microbiologically evaluable (ME) subjects with cSSSI are presented in Table 5.

Table 5. Clinical Cure Rates by Infecting Pathogen in ME Subjects with cSSSI[a]

Pathogen	Tigecycline n/N (%)	Vancomycin/ Aztreonam n/N (%)
Escherichia coli	29/36 (80.6)	26/30 (86.7)
Enterobacter cloacae	10/12 (83.3)	15/15 (100)
Enterococcus faecalis (vancomycin-susceptible only)	15/21 (71.4)	19/24 (79.2)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)[b]	124/137 (90.5)	113/120 (94.2)
Methicillin-resistant *Staphylococcus aureus* (MRSA)[b]	79/95 (83.2)	46/57 (80.7)
CA-MRSA[c]	13/20 (65.0)	10/12 (83.3)
Streptococcus agalactiae	8/8 (100)	11/14 (78.6)
Streptococcus anginosus grp.[d]	17/21 (81.0)	9/10 (90.0)
Streptococcus pyogenes	31/32 (96.9)	24/27 (88.9)
Bacteroides fragilis	7/9 (77.8)	4/5 (80.0)

[a] Two pivotal studies from cSSSI and two Phase 3 Resistant Pathogen studies.
[b] Includes cases of concurrent bacteremia.
[c] CA-MRSA = community acquired (MRSA isolates that bear molecular and virulence markers commonly associated with community acquired MRSA, including SCCmec type IV element and the pvl gene).
[d] Includes *Streptococcus anginosus, Streptococcus intermedius,* and *Streptococcus constellatus.*

Tigecycline did not meet non-inferiority criteria in comparison with ertapenem in a study of subjects with diabetic foot infection (see Table 6). This was a randomized, double-blind, multinational, multicenter trial comparing tigecycline (150 mg every 24 hours) with ertapenem (1 g every 24 hours, with or without vancomycin) for up to 28 days. The primary efficacy endpoint was the clinical response at the TOC assessment in the co-primary CE and c-mITT populations. The non-inferiority margin was -10% for the difference in cure rates between the 2 treatments.

Table 6. Clinical Cure Rates in Subjects with Diabetic Foot Infection After up to 28 Days of Therapy		
	Tigecycline[a] n/N (%)	Ertapenem[b] (± Vancomycin) n/N (%)
CE	316/408 (77.5%)[c]	334/405 (82.5%)[c]
c-mITT	340/476 (71.4%)[d]	363/466 (77.9%)[d]

[a] 150 mg once every 24 hours.
[b] 1 g once every 24 hours.
[c] Adjusted difference = -5.5; 95% CI = -11.0, 0.1.
[d] Adjusted difference = -6.7; 95% CI = -12.3, -1.1.

Complicated Intra-abdominal Infections (cIAI)

Tigecycline was evaluated in adults for the treatment of cIAI in two randomized, double-blind, active-controlled, multinational, multicenter studies. These studies compared tigecycline (100 mg IV initial dose followed by 50 mg every 12 hours) with imipenem/cilastatin (500 mg IV every 6 hours) for 5 to 14 days. Subjects with complicated diagnoses including appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of the intestine, and peritonitis were enrolled in the studies. The primary efficacy endpoint was the clinical response at the TOC visit for the co-primary populations of the ME and the microbiologic modified intent-to-treat (m-mITT) subjects. See Table 7.

Table 7. Clinical Cure Rates from Two Pivotal Studies in cIAI

	Tigecycline[a] n/N (%)	Imipenem/ Cilastatin[b] n/N (%)
ME	441/512 (86.1)	442/513 (86.2)
m-mITT	506/631 (80.2)	514/631 (81.5)

[a] 100 mg initially, followed by 50 mg every 12 hours.
[b] Imipenem/Cilastatin (500 mg every 6 hours).

Clinical cure rates at TOC by pathogen in ME subjects with cIAI are presented in Table 8.

Table 8. Clinical Cure Rates by Infecting Pathogen in ME Subjects with cIAI[a]

Pathogen	Tigecycline n/N (%)	Imipenem/ Cilastatin n/N (%)
Citrobacter freundii	12/16 (75.0)	3/4 (75.0)
Enterobacter cloacae	15/17 (88.2)	16/17 (94.1)
Escherichia coli	284/336 (84.5)	297/342 (86.8)
Klebsiella oxytoca	19/20 (95.0)	17/19 (89.5)
Klebsiella pneumoniae[b]	42/47 (89.4)	46/53 (86.8)
Enterococcus faecalis	29/38 (76.3)	35/47 (74.5)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)[c]	26/28 (92.9)	22/24 (91.7)
Methicillin-resistant *Staphylococcus aureus* (MRSA)[c]	16/18 (88.9)	1/3 (33.3)
Streptococcus anginosus grp.[d]	101/119 (84.9)	60/79 (75.9)

Bacteroides fragilis	68/88 (77.3)	59/73 (80.8)
Bacteroides thetaiotaomicron	36/41 (87.8)	31/36 (86.1)
Bacteroides uniformis	12/17 (70.6)	14/16 (87.5)
Bacteroides vulgatus	14/16 (87.5)	4/6 (66.7)
Clostridium perfringens	18/19 (94.7)	20/22 (90.9)
Peptostreptococcus micros	13/17 (76.5)	8/11 (72.7)

[a] Two cIAI pivotal studies and two Phase 3 Resistant Pathogen studies.
[b] Includes ESBL producing isolates.
[c] Includes cases of concurrent bacteremia.
[d] Includes *Streptococcus anginosus, Streptococcus intermedius,* and *Streptococcus constellatus.*

Community Acquired Pneumonia (CAP)

Tigecycline was evaluated in adults for the treatment of CAP in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 308 and 313). These studies compared tigecycline (100 mg IV initial dose followed by 50 mg every 12 hours) with levofloxacin (500 mg IV every 12 or 24 hours). In one study (Study 308), after at least 3 days of IV therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms. Total therapy was 7 to 14 days. Subjects with CAP who required hospitalization and IV therapy were enrolled in the studies. The primary efficacy endpoint was the clinical response at the TOC visit in the co-primary populations of the CE and c-mITT subjects. See Table 9. Clinical cure rates at TOC by pathogen in the ME subjects are presented in Table 10.

Table 9. Clinical Cure Rates from Two Pivotal Studies in CAP after 7 to 14 Days of Total Therapy

	Tigecycline[a] n/N (%)	Levofloxacin[b] n/N (%)
Integrated		
CE	253/282 (89.7)	252/292 (86.3)
c-mITT	319/394 (81.0)	321/403 (79.7)
Study 308		
CE	125/138 (90.6)	136/156 (87.2)
c-mITT	149/191 (78.0)	158/203 (77.8)
Study 313		
CE	128/144 (88.9)	116/136 (85.3)
c-mITT	170/203 (83.7)	163/200 (81.5)

[a] 100 mg initially, followed by 50 mg every 12 hours.
[b] Levofloxacin (500 mg IV every 12 or 24 hours); in one study (Study 308), after at least 3 days of IV therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms.

Table 10. Clinical Cure Rates by Infecting Pathogen in ME Subjects with CAP[a]

Pathogen	Tigecycline n/N (%)	Levofloxacin n/N (%)
Chlamydia pneumoniae	18/19 (94.7)	26/27 (96.3)
Haemophilus influenzae	14/17 (82.4)	13/16 (81.3)
Legionella pneumophila	10/10 (100.0)	6/6 (100.0)
Moraxella catarrhalis	3/3 (100.0)	3/5 (60.0)
Mycoplasma pneumoniae	37/39 (94.9)	44/48 (91.7)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	9/12 (75.0)	8/10 (80.0)
Streptococcus pneumoniae (penicillin-susceptible only)[b]	44/46 (95.7)	39/44 (88.6)

Table 10. Clinical Cure Rates by Infecting Pathogen in ME Subjects with CAP[a]

Pathogen	Tigecycline n/N (%)	Levofloxacin n/N (%)

[a] Two CAP pivotal studies.
[b] Includes cases of concurrent bacteremia.

Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Vancomycin-Resistant *Enterococcus (VRE)* spp.

Tigecycline was evaluated in adults for the treatment of various serious infections (cIAI, cSSSI, and other infections) due to VRE and MRSA in Study 307.

Study 307 was a randomized, double-blind, active-controlled, multinational, multicenter study evaluating tigecycline (100 mg IV initial dose followed by 50 mg every 12 hours) and vancomycin (1 g IV every 12 hours) for the treatment of infections due to MRSA and evaluating tigecycline (100 mg IV initial dose followed by 50 mg every 12 hours) and linezolid (600 mg IV every 12 hours) for the treatment of infections due to VRE for 7 to 28 days. Subjects with cIAI, cSSSI, and other infections were enrolled in this study. The primary efficacy endpoint was the clinical response at the TOC visit for the co-primary populations of the ME and the m-mITT subjects. For clinical cure rates, see Table 11 for MRSA and Table 12 for VRE.

Table 11. Clinical Cure Rates from Resistant Pathogen Study 307[a] for MRSA after 7 to 28 Days of Therapy

	Tigecycline[b] n/N (%)	Vancomycin[c] n/N (%)
Study 307		
ME	70/86 (81.4)	26/31 (83.9)
cIAI	13/14 (92.9)	4/4 (100.0)
cSSSI	51/59 (86.4)	20/23 (87.0)
m-mITT	75/100 (75.0)	27/33 (81.8)
cIAI	13/15 (86.7)	5/6 (83.3)
cSSSI	55/70 (78.6)	20/23 (87.0)

[a] Study included subjects with cIAI, cSSSI, and other infections.
[b] 100 mg initially, followed by 50 mg every 12 hours.
[c] 1 g IV every 12 hours.

Table 12. Clinical Cure Rates from Resistant Pathogen Study 307[a] for VRE after 7 to 28 Days of Therapy

	Tigecycline[b] n/N (%)	Linezolid[c] n/N (%)
Study 307		
ME	3/3 (100.0)	2/3 (66.7)
cIAI	1/1 (100.0)	0/1 (0.0)
cSSSI	1/1 (100.0)	2/2 (100.0)
m-mITT	3/8 (37.5)	2/3 (66.7)
cIAI	1/2 (50.0)	0/1 (0.0)
cSSSI	1/2 (50.0)	2/2 (100.0)

[a] Study included subjects with cIAI, cSSSI, and other infections.
[b] 100 mg initially, followed by 50 mg every 12 hours.
[c] Linezolid (600 mg IV every 12 hours).

Resistant Gram-Negative Pathogens

Tigecycline was evaluated in adults for the treatment of various serious infections (cIAI, cSSSI, CAP, and other infections) due to resistant gram-negative pathogens in Study 309.

Study 309 was an open-label, multinational, multicenter study evaluating tigecycline (100 mg IV initial dose followed by 50 mg every 12 hours) for the treatment of infections due to resistant gram-negative pathogens for 7 to 28 days. Subjects with cIAI, cSSSI, CAP, and other infections were enrolled in this study. The primary efficacy endpoint was the clinical response at the TOC visit for the co-primary populations of the ME and the m-mITT subjects. See Table 13.

Table 13. Clinical Cure Rates from Resistant Pathogen Study 309[a] for Resistant Gram-negative Pathogens after 5 to 28 Days of Therapy

		Tigecycline[b] n/N (%)	Tigecycline[b] n/N (%)	Tigecycline[b] n/N (%)
Study 309	All[c]	*E. coli*	*Klebsiella pneumoniae*	*Enterobacter* spp.
ME	26/36 (72.2)	4/9 (44.4)	5/6 (83.3)	3/4 (75.0)
cIAI	2/2 (100.0)[d]	1/1 (100.0)[d]	1/1 (100.0)	-
cSSSI	20/24 (83.3)	3/5 (60.0)	3/3 (100.0)	3/3 (100.0)
CAP	0/1 (0.0)	-	-	0/1 (0.0)
m-mITT	40/75 (53.3)	5/10 (50.0)	9/13 (69.2)	8/15 (53.3)
cIAI	6/9 (66.7)[d]	2/2 (100.0)[d]	1/1 (100.0)	1/1 (100.0)[d]
cSSSI	27/38 (71.1)	3/5 (60.0)	6/7 (85.7)	7/8 (87.5)
CAP	0/1 (0.0)	-	-	0/1 (0.0)

[a] Study included subjects with cIAI, cSSSI, CAP and other infections.
[b] 100 mg initially, followed by 50 mg every 12 hours.
[c] Includes other pathogens besides *E. coli, Klebsiella pneumoniae*, and *Enterobacter* spp.
[d] Excludes subjects with inadequate source control.

Rapidly Growing Mycobacterial Infections

In uncontrolled clinical studies and compassionate-use experience from 8 countries, 52 subjects with rapidly-growing mycobacterial infections (most frequently *M. abscessus* lung disease) were treated with tigecycline, along with other antibiotics. The mean and

median durations of treatment were approximately 5½ months and 3 months, respectively (range: 3 days to approximately 3½ years). Approximately half of the subjects achieved clinical improvement (i.e., improvement in signs and symptoms of lung disease, or healing of wound, skin lesions, or nodules in disseminated disease). Approximately half of the subjects required dose reductions or discontinued treatment due to nausea, vomiting, or anorexia.

Pediatric population

In an open-label, ascending multiple-dose study, 39 children aged 8 to 11 years with cIAI or cSSSI were administered tigecycline (0.75, 1, or 1.25 mg/kg). All patients received IV tigecycline for a minimum of 3 consecutive days to a maximum of 14 consecutive days, with the option to be switched to an oral antibiotic on or after day 4.

Clinical cure was assessed between 10 and 21 days after the administration of the last dose of treatment. The summary of clinical response in the modified intent-to-treat (mITT) population results is shown in the following table.

Clinical Cure, mITT Population			
	0.75 mg/kg	1 mg/kg	1.25 mg/kg
Indication	n/N (%)	n/N (%)	n/N (%)
cIAI	6/6 (100.0)	3/6 (50.0)	10/12 (83.3)
cSSSI	3/4 (75.0)	5/7 (71.4)	2/4 (50.0)
Overall	9/10 (90.0)	8/13 (62.0 %)	12/16 (75.0)

Efficacy data shown above should be viewed with caution as concomitant antibiotics were allowed in this study. In addition, the small number of patients should also be taken into consideration.

Cardiac Electrophysiology
No significant effect of a single intravenous dose of tigecycline 50 mg or 200 mg on QTc interval was detected in a randomized, placebo- and active-controlled four-arm crossover thorough QTc study of 46 healthy subjects.

5.2 Pharmacokinetic properties

The mean pharmacokinetic parameters of tigecycline for the recommended dosage regimen after single and multiple intravenous doses are summarized in Table 14.

Intravenous infusions of tigecycline should be administered over approximately 30 to 60 minutes.

Table 14. Mean (CV%) Pharmacokinetic Parameters of Tigecycline		
	Single Dose	Multiple Dose[c]
	100 mg	50 mg q12h
C_{max} (µg/mL)[a]	1.45 (22%)	0.87 (27%)
C_{max} (µg/mL)[b]	0.90 (30%)	0.63 (15%)
AUC (µg·h/mL)	5.19 (36%)	-
AUC_{0-24h} (µg·h/mL)	-	4.70 (36%)
C_{min} (µg/mL)	-	0.13 (59%)
$t_{½}$ (h)	27.1 (53%)	42.4 (83%)
CL (L/h)	21.8 (40%)	23.8 (33%)
CL_r (mL/min)	38.0 (82%)	51.0 (58%)
V_{ss} (L)	568 (43%)	639 (48%)
[a] 30-minute infusion. [b] 60-minute infusion. [c] 100 mg initially, followed by 50 mg every 12 hours.		

Absorption
Tigecycline is administered intravenously, and therefore has 100% bioavailability.

Distribution
The *in vitro* plasma protein binding of tigecycline ranges from approximately 71% to 89% at concentrations observed in clinical studies (0.1 to 1.0 µg/mL). Animal and human pharmacokinetic studies have demonstrated that tigecycline readily distributes to tissues. In rats receiving single or multiple doses of C-tigecycline, radioactivity was well distributed to most tissues, with the highest overall exposure observed in bone, bone marrow, thyroid gland, kidney, spleen, and salivary gland. In humans, the steady-state volume of distribution of tigecycline averaged 500 to 700 L (7 to 9 L/kg), indicating tigecycline is extensively distributed beyond the plasma volume and into the tissues of humans.

Two studies examined the steady-state pharmacokinetic profile of tigecycline in specific tissues or fluids of healthy subjects receiving tigecycline 100 mg followed by 50 mg every 12 hours. In a bronchoalveolar lavage study, the tigecycline AUC_{0-12h} (134 µg·h/mL) in alveolar cells was approximately 77.5-fold higher than the AUC_{0-12h} in the serum of these subjects, and the AUC_{0-12h} (2.28 µg·h/mL) in epithelial lining fluid was approximately 32% higher than the AUC_{0-12h} in serum. In a skin blister study, the AUC_{0-12h} (1.61 µg·hr/mL) of tigecycline in skin blister fluid was approximately 26% lower than the AUC_{0-12h} in the serum of these subjects.

In a single-dose study, tigecycline 100 mg was administered to subjects prior to undergoing elective surgery or medical procedure for tissue extraction. Tissue concentrations at 4 hours after tigecycline administration were measured in the following tissue and fluid samples: gallbladder, lung, colon, synovial fluid, and bone. Tigecycline attained higher concentrations in tissues versus serum in gallbladder (38-fold, n=6), lung (3.7-fold, n=5), and colon (2.3-fold, n=6). The concentration of tigecycline in these tissues after multiple doses has not been studied.

Metabolism
Tigecycline is not extensively metabolized. *In vitro* studies with tigecycline using human liver microsomes, liver slices, and hepatocytes led to the formation of only trace amounts of metabolites. In healthy male volunteers, receiving ^{14}C-tigecycline, tigecycline was the primary ^{14}C-labeled material recovered in urine and feces, but a glucuronide, an N-acetyl metabolite and a tigecycline epimer (each at no more than 10% of the administered dose) were also present.

Elimination
The recovery of total radioactivity in feces and urine following administration of ^{14}C-tigecycline indicates that 59% of the dose is eliminated by biliary/fecal excretion, and 33% is excreted in urine. Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline. Glucuronidation and renal excretion of unchanged tigecycline are secondary routes.

Tigecycline is a substrate of P-gp based on an *in vitro* study using a cell line overexpressing P-gp. The potential contribution of P-gp-mediated transport to the *in vivo* disposition of tigecycline is not known.

Special populations

Hepatic insufficiency

In a study comparing 10 subjects with mild hepatic impairment (Child-Pugh A), 10 subjects with moderate hepatic impairment (Child-Pugh B), and five subjects with severe hepatic impairment (Child-Pugh C) to 23 age- and weight-matched healthy control subjects, the single-dose pharmacokinetic disposition of tigecycline was not altered in subjects with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25%, and the half-life of tigecycline was prolonged by 23% in subjects with moderate hepatic impairment (Child-Pugh B). In addition, systemic clearance of tigecycline was reduced by 55%, and the half-life of tigecycline was prolonged by 43% in subjects with severe hepatic impairment (Child-Pugh C).

Based on the pharmacokinetic profile of tigecycline, no dosage adjustment is warranted in subjects (including pediatrics) with mild to moderate hepatic impairment (Child-Pugh A and Child-Pugh B). However, in subjects with severe hepatic impairment (Child-Pugh C), the dose of tigecycline should be reduced by 50%. Adult dose should be altered to 100 mg followed by 25 mg every 12 hours. Subjects with severe hepatic impairment (Child-Pugh C) should be treated with caution and monitored for treatment response (see Section **4.2 Dosage and method of administration**).

Renal insufficiency

A single-dose study compared 6 subjects with severe renal impairment (creatinine clearance ClCr ≤30 mL/min), 4 end stage renal disease subjects receiving tigecycline 2 hours before hemodialysis, 4 end stage renal disease subjects receiving tigecycline after hemodialysis, and 6 healthy control subjects. The pharmacokinetic profile of tigecycline was not altered in any of the renally-impaired subjects groups, nor was tigecycline removed by hemodialysis. No dosage adjustment of tigecycline is necessary in subjects with renal impairment or in subjects undergoing hemodialysis (see Section **4.2 Dosage and method of administration**).

Elderly

No overall differences in pharmacokinetics were observed between healthy elderly subjects (n=15, age 65-75; n=13, age >75, and younger subjects (n=18) receiving a single, 100 mg dose of tigecycline. Therefore, no dosage adjustment is necessary based on age.

Children

Tigecycline pharmacokinetics were investigated in two studies. The first study enrolled children aged 8-16 years (n=24) who received single doses of tigecycline (0.5, 1, or 2 mg/kg, up to a maximum dose of 50 mg, 100 mg, and 150 mg, respectively) administered intravenously over 30 minutes. The second study was performed in children aged 8 to 11 years who received multiple doses of tigecycline (0.75, 1, or 1.25 mg/kg up to a maximum dose of 50 mg) every 12 hours administered intravenously over 30 minutes. No loading dose was administered in these studies. Pharmacokinetic parameters are summarized in the table below.

Dose Normalized to 1 mg/kg Mean ± SD Tigecycline C_{max} and AUC in Children			
Age (yr)	N	C_{max} (ng/mL)	AUC (ng•h/mL)*
Single dose			
8 – 11	8	3881 ± 6637	4034 ± 2874
12 – 16	16	8508 ± 11433	7026 ± 4088
Multiple dose			
8 – 11	42	1911 ± 3032	2404 ± 1000
* Single dose $AUC_{0-\infty}$,, multiple dose AUC_{0-12h}			

The target AUC_{0-12h} in adults after the recommended dose of 100 mg loading and 50 mg every 12 hours, was approximately 2500 ng•h/mL.

Population PK analysis of both studies identified body weight as a covariate of tigecycline clearance in children aged 8 years and older. A dosing regimen of 1.2 mg/kg of tigecycline every 12 hours (to a maximum dose of 50 mg every 12 hours) for children aged 8 to <12 years, and of 50 mg every 12 hours for adolescents aged 12 to <18 years would likely result in exposures comparable to those observed in adults treated with the approved dosing regimen.

Gender

In a pooled analysis of 38 women and 298 men participating in clinical pharmacology studies, there was no significant difference in the mean (±SD) tigecycline clearance between women (20.7±6.5 L/h) and men (22.8±8.7 L/h). Therefore, no dosage adjustment is necessary based on gender.

Race

In a pooled analysis of 73 Asian subjects, 53 Black subjects, 15 Hispanic subjects, 190 White subjects, and 3 subjects classified as "other" participating in clinical pharmacology studies, there was no significant difference in the mean (±SD) tigecycline clearance among the Asian subjects (28.8±8.8 L/h), Black subjects (23.0±7.8 L/h), Hispanic subjects (24.3±6.5 L/h), White subjects (22.1±8.9 L/h), and "other" subjects (25.0±4.8 L/h). Therefore, no dosage adjustment is necessary based on race.

5.3 Preclinical Safety Data

Carcinogenicity

Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of tigecycline.

Mutagenicity

No mutagenic or clastogenic potential was found in a battery of tests, including an *in vitro* chromosome aberration assay in Chinese hamster ovary (CHO) cells, *in vitro* forward mutation assay in CHO cells (HGRPT locus), *in vitro* forward mutation assays in mouse lymphoma cells, and *in vivo* micronucleus assay.

Reproduction toxicity

Tigecycline did not affect mating or fertility in rats at exposures up to 4.7 times the human daily dose based on AUC. In female rats, there were no compound-related effects on ovaries or estrus cycles at exposures up to 4.7 times the human daily dose based on AUC.

In preclinical safety studies, ^{14}C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of tigecycline was associated with slight reductions in fetal weights and an increased incidence of minor skeletal anomalies (delays in bone ossification) at exposures of 4.7 times and 1.1 times the human daily dose based on AUC in rats and rabbits, respectively.

Results from animal studies using ^{14}C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in the

nursing pups as a result of exposure via the maternal milk.

Other

Decreased erythrocytes, reticulocytes, leukocytes and platelets, in association with bone marrow hypocellularity, have been seen with tigecycline at exposures of 8.1 times and 9.8 times the human daily dose based on AUC in rats and dogs, respectively. These alterations were shown to be reversible after two weeks of dosing.

Bolus intravenous administration of tigecycline has been associated with a histamine response in preclinical studies. These effects were observed at exposures of 14.3 and 2.8 times the human daily dose based on the AUC in rats and dogs, respectively.

No evidence of photosensitivity was observed in rats following administration of tigecycline.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life

Please see outer package or vial label for the expiration date.

6.2 Storage conditions

Tigecycline should be stored at temperatures not exceeding 30°C prior to reconstitution. Once reconstituted, tigecycline may be stored at room temperature (not to exceed 25°C) for up to 24 hours (up to 6 hours in the vial and the remaining time in the IV bag). Alternatively, tigecycline mixed with 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, may be stored refrigerated at 2°C to 8°C for up to 48 hours following immediate transfer of the reconstituted solution into the IV bag.

If the storage conditions exceed 25°C after reconstitution, tigecycline should be used immediately.

6.3 Availability

Type I Clear Glass Vial x 5 mL with orange flip-off seal (Box of 1's)

6.4 Incompatibilities

Compatible intravenous solutions include 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, and Lactated Ringer's Injection, USP.

Tigecycline is compatible with the following drugs or diluents when used with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP and administered simultaneously through the same line: amikacin, dobutamine, dopamine HCl, gentamicin, haloperidol, Lactated Ringer's, lidocaine HCl, metoclopramide, morphine,

norepinephrine, piperacillin/tazobactam (EDTA formulation), potassium chloride, propofol, ranitidine HCl, theophylline, and tobramycin.

The following drugs should not be administered simultaneously through the same line as tigecycline: amphotericin B, amphotericin B lipid complex, diazepam, esomeprazole and omeprazole.

6.5 Special precautions for disposal and other handling

The lyophilized powder should be reconstituted with 5.3 mL of 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, or Lactated Ringer's Injection, USP, to achieve a concentration of 10 mg/mL of tigecycline. The vial should be gently swirled until the drug dissolves. Withdraw 5 mL of the reconstituted solution from the vial and add to a 100 mL IV bag for infusion. For a 100 mg dose, reconstitute using two vials into a 100 mL IV bag. (Note: The vial contains a 6% overage. Thus, 5 mL of reconstituted solution is equivalent to 50 mg of the drug.) The reconstituted solution should be yellow to orange in color; if not, the solution should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration (e.g., green or black) prior to administration whenever solution and container permit. Once reconstituted, tigecycline may be stored at room temperature (not to exceed 25°C) for up to 24 hours (up to 6 hours in the vial and the remaining time in the IV bag). Alternatively, tigecycline mixed with 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP may be stored refrigerated at 2°C to 8°C for up to 48 hours following immediate transfer of the reconstituted solution into the IV bag.

If the storage conditions exceed 25°C after reconstitution, tigecycline should be used immediately.

Tigecycline may be administered intravenously through a dedicated line or through a Y-site. If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of tigecycline with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. Injection should be made with an infusion solution compatible with tigecycline and with any other drug(s) administered via this common line (see Section **6.2 Incompatibilities**).

7. FDA REGISTRATION NUMBER

DR-XY39444

8. DATE OF FIRST AUTHORIZATION

09 October 2013

Keep out of reach of children

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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Revision No.: 9.1
Revision Date: 14 May 2024
Reference Document: CDS ver 27/BOH approval with changes
Reference Date: 01 December 2020/13 Jul 2022