PRODUCT MONOGRAPH

Pr TIGECYCLINE

Tigecycline for Injection

Sterile, lyophilized powder for intravenous use

50 mg/vial

Professed

Tetracycline Antibiotic (glycylcycline derivative)

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Control Number: 158755

DATE OF PREPARATION:
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[Pr] TIGECYCLINE
Tigecycline for Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY OF PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients*
Intravenous infusion	Sterile, lyophilized powder 50 mg tigecycline per vial	Lactose monohydrate

* (See Dosage Forms, Composition and Packaging).

INDICATIONS AND CLINICAL USE

TIGECYCLINE (tigecycline) is indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms in patients 18 years of age and older:

- Complicated skin and skin structure infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible strains only), *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus agalactiae, Streptococcus anginosus*, *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis.*

  Patients with severe underlying disease, such as those who were immunocompromised, patients with decubitus ulcer infections, or patients who had infections requiring longer than 14 days of treatment (for example, necrotizing fasciitis), were not enrolled in clinical trials.

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

- Community *acquired pneumonia* (mild to moderate infections only) *caused by Haemophilus influenzae, Streptococcus pneumoniae* (penicillin-susceptible isolates only), *Mycoplasma pneumoniae, and Chlamydia pneumoniae.*

  Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to tigecycline. Once these results are available, antimicrobial therapy should be adjusted if necessary. TIGECYCLINE may be initiated as empiric therapy before results of these tests are known.

Tigecycline has decreased *in vitro* activity against *Proteus spp., Providencia spp., and Morganella spp. Pseudomonas aeruginosa* is inherently resistant to TIGECYCLINE.

Geriatrics (≥ 65 years of age): Evidence from clinical studies suggests that **use** in the geriatric population is not associated with differences in safety or effectiveness. A brief discussion can be found in **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**.

Pediatrics (<18 years of age): No data is available. (See **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

CONTRAINDICATIONS

TIGECYCLINE is contraindicated for use in patients who have known hypersensitivity to tigecycline or tetracycline class of antibiotics.

WARNINGS AND PRECAUTIONS

All-Cause Mortality

An increase in all-cause mortality has been observed across Phase 3 and 4 clinical trials in tigecycline-treated patients versus comparator-treated patients. In a pooled analysis of all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of patients receiving tigecycline and 3.0% (110/3646) of patients receiving comparator drugs. 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 patients. The cause of this increase has not been established. This increase in all-cause mortality should be considered when selecting among treatment options. (See **ADVERSE REACTIONS**).

General

Anaphylaxis/anaphylactoid reactions have been reported with TIGECYCLINE, and may be life-threatening.

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

Acute pancreatitis, including fatal cases, have occurred in association with tigecycline treatment (See **ADVERSE REACTIONS**). The diagnosis of acute pancreatitis should be considered in patients taking tigecycline who develop clinical symptoms, signs, or laboratory abnormalities suggestive of acute pancreatitis. 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 cases suspected of having developed pancreatitis.

Tigecycline may be associated with permanent tooth discoloration in humans during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years). Results of studies in rats with tigecycline have shown bone discoloration.

During antibiotic therapy, colonization or superinfection with *Candida*, *Proteus* or *Pseudomonas* spp may occur in the GI, genitourinary, and respiratory tracts. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

TIGECYCLINE is **not** indicated for the treatment of diabetic foot infections. The safety and efficacy of TIGECYCLINE in patients with diabetic foot infections have not been established.

TIGECYCLINE is **not** indicated for the treatment of severe community acquired pneumonia. Safety and efficacy of TIGECYCLINE in severe community acquired pneumonia have not been studied. (See **CLINICAL TRIALS**). TIGECYCLINE has not been evaluated in clinical trials for use against suspected or documented multiple drug resistant pathogens in pneumonia.

TIGECYCLINE is **not** indicated for treatment of hospital acquired pneumonia. The safety and efficacy of TIGECYCLINE in patients with hospital acquired pneumonia have not been established. In a study of hospital acquired pneumonia patients, the sub-group of patients with ventilator-associated pneumonia 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 patients with ventilator-associated pneumonia and bacteremia at baseline, those who received TIGECYCLINE had greater mortality (9/18 [50.0%] versus 1/13 [7.7%]) than the comparator.

Caution should be exercised when considering tigecycline monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. (See **ADVERSE REACTIONS**). In Phase 3 cIAI studies (n=1642), 6 patients treated with tigecycline and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with tigecycline had higher APACHE II scores (median = 13) vs the 2 patients treated with imipenem/cilastatin (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.

Cardiovascular

An effect on cardiac repolarization following tigecycline administration cannot be definitively excluded from the clinical data. (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Cardiovascular**).

There is limited clinical experience using tigecycline in patients with known prolongation of the QTc interval, patients with hypokalemia, patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents, or in other proarrhythmic conditions.

Pharmacokinetic studies between tigecycline and drugs that prolong the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. The effect of tigecycline has also not been studied in patients with congenital prolongation of the QT interval. It is expected that these individuals may be more susceptible to drug-induced QT prolongation.

The magnitude of QTc prolongation may increase with increasing concentrations of drugs; therefore, the recommended dose and the recommended infusion rate for tigecycline should not be exceeded. (see **DOSAGE AND ADMINISTRATION**).

Patients should be instructed to contact their physician if they experience palpitations or fainting spells while taking tigecycline.

Gastrointestinal

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including tigecycline. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases. (see **ADVERSE REACTIONS).**

Hepatic/Biliary/Pancreatic

Increases in total bilirubin concentration, prothrombin time and transaminases have been seen in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients treated with tigecycline. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing tigecycline therapy. Adverse events may occur after the drug has been discontinued.

Cases of pancreatitis have been reported.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies of tigecycline in pregnant women. Tigecycline should not be used unless the potential benefit to the mother outweighs any possible risk to the fetus.

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. Tigecycline was not teratogenic in the rat or rabbit. Decreased fetal weights and increased incidence of minor skeletal anomalies in rats and rabbits (with associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline. (See **TOXICOLOGY**).

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

Nursing Women: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and there is the potential risk of permanent discoloration of the teeth/bones (yellow gray- brown) of the child, tigecycline should not be administered to a nursing woman unless the potential benefit to the mother outweighs any possible risk to the child. (See **WARNINGS AND PRECAUTIONS, General**).

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

Pediatrics (< 18 years of age): Tigecycline should not be used in children under 8 years of age because of the risk of teeth discoloration. Safety and effectiveness in pediatric patients below the age of 18 have not been established. Therefore, use in patients under 18 years of age is not recommended.

Geriatrics (≥ 65 years of age): Of the total number of subjects who received tigecycline in Phase 3 clinical studies (n=2514), 664 were 65 years of age and over, while 288 were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events in some older individuals cannot be ruled out.

Monitoring and Laboratory Tests

Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin.

Occupational Hazards

Driving a vehicle or operating machinery

Tigecycline can cause dizziness which may impair the ability to drive and/or operate machinery.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The overall incidence of drug-related adverse reactions with tigecycline was 41.0%. The most common adverse drug reactions, as judged by investigators, in patients treated with tigecycline were nausea at 18.9% (11.6% mild; 6.4% moderate; 0.9% severe) and vomiting 12.4% (7.4% mild; 4.3% moderate; 0.6% severe). In general, nausea and vomiting occurred early in treatment (days 1 – 2) and on average over 2 to 4 days.

Tigecycline was discontinued due to an adverse event in 6.7% of subjects. Discontinuation from tigecycline was most frequently associated with nausea (1.1%) and vomiting (1.1%).

Clinical Trial Adverse Drug Reactions

Because clinical studies are conducted under varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates

In Phase 3 clinical studies, 2514 patients were treated with tigecycline. These patients received at least 1 dose of tigecycline. In the active controlled studies that employed a 1:1 randomization, 2274 patients with complicated intra-abdominal infections, complicated skin and skin structure infections, community acquired pneumonia, and hospital acquired pneumonia were treated with tigecycline for up to 14 days (see CLINICAL TRIALS). In resistant pathogen clinical studies which were uncontrolled or employed a randomization of 3:1, 184 patients were treated for up to 14 days and 56 patients up to 28 days.

Table 1 shows the incidence (%) of treatment-emergent adverse drug reactions (as judged by the investigators) reported in ≥1% of patients treated with tigecycline in Phase 3 clinical studies.

Table 1: Incidence (%) of Adverse Drug Reactions Reported in ≥1% of Patients Treated with tigecycline in Phase 3 Clinical Studies

Adverse Events	Tigecycline[a] (N=2514)	Comparator (N=2307)
Any adverse event	41.0	32.4
Body as a whole	6.2	6.1
Abdominal pain	1.2	0.6
Headache	1.2	1.7
Cardiovascular system	3.7	5.0
Phlebitis	1.5	2.3
Digestive system	27.2	14.9
Nausea	18.9	7.8
Vomiting	12.4	4.2
Diarrhea	6.2	4.9
Anorexia	1.1	0.2
Liver function tests abnormal	1.0	0.8
Hemic and lymphatic system	6.0	5.0
Thrombocythemia	2.1	1.8
Activated partial thromboplastin time prolonged	1.0	0.4
Metabolic and nutritional	8.7	7.5

Lactic dehydrogenase increased	1.4	1.0
Alkaline phosphatase increased	1.9	1.5
SGPT increased[b]	2.5	3.4
SGOT increased[b]	2.2	3.3
Amylase increased	1.4	1.0
Bilirubinemia	1.3	0.2
Skin and appendages	2.7	3.8
Rash	1.2	1.7
Urogenital system	1.4	0.8
Vaginal moniliasis	1.0	0.6

a. 100 mg initially, followed by 50 mg every 12 hours.
b. Liver function test abnormalities in tigecycline-treated patients were reported more frequently in the posttherapy period than those in comparator-treated patients, which occurred more often on therapy.
Abbreviations: SGPT=serum glutamic pyruvic transaminase; SGOT=serum glutamic oxaloacetic transaminase.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse drug reactions as judged by the investigators were reported infrequently (<1% and ≥0.1%) in patients receiving tigecycline in Phase 3 clinical studies:

Body as a whole: infection, fever, asthenia, septic shock, injection site inflammation, injection site pain, injection site reaction, chills, injection site edema, injection site phlebitis, pain, moniliasis, chest pain, chills and fever, malaise, peritonitis, allergic reaction

Cardiovascular system: thrombophlebitis, hypertension, hypotension, bradycardia, vasodilatation, tachycardia, atrial fibrillation, AV block first degree, congestive heart failure, electrocardiogram abnormal, palpitation, QT interval prolonged, sinus bradycardia, syncope, tachycardia sinus, ventricular extrasystoles

Digestive system: dyspepsia, oral moniliasis, constipation, dry mouth, jaundice, stools abnormal, abdominal distension, fecal incontinence, flatulence, gastroesophageal reflux disease, glossitis, hepatic failure, liver damage, mucositis, pancreatitis, pseudomembranous colitis

Hemic and lymphatic system: eosinophilia, prothrombin time prolonged, anemia, leukocytosis, leukopenia, international normalized ratio increased, thrombocytopenia, coagulation disorder, ecchymosis, hemolysis, neutropenia, prothrombin decreased, prothrombin time shortened

Metabolic and nutritional: BUN increased, hypoproteinemia, creatinine increased, hypocalcemia, hyperkalemia, hyponatremia, peripheral edema, hypoglycemia, hypokalemia, creatine phosphokinase increased, healing abnormal, hyperglycemia, hyperphosphatemia, hypophosphatemia

Musculoskeletal system: myalgia

Nervous system: dizziness, somnolence, insomnia, nervousness, tremor, twitching, vertigo

Respiratory system: cough increased, dyspnea, hiccup, pleural effusion, pneumonia, pulmonary physical finding, pharyngitis, sputum increased

Skin and appendages: pruritus, sweating, urticaria, fungal dermatitis, herpes simplex, maculopapular rash, pruritic rash, skin discoloration

Special senses: taste perversion, abnormal vision

Urogenital system: vaginitis, kidney function abnormal, urinary tract infection, creatinine clearance decreased, leukorrhea, polyuria, scrotal edema, vulvovaginal disorder, vulvovaginitis
Adverse events associated with miscellaneous factors: local reaction to procedure, device malfunction

In addition to those noted above, the following adverse reactions judged as related as determined by the investigator were noted in Phase 2 studies in complicated skin and skin structure infections and complicated intra-abdominal infections: hypomagnesemia, confusion.

Adverse reactions for the Phase 1 clinical pharmacology studies are similar to those reported in Phase 3 and Phase 2 clinical trials. The most common adverse reactions in these trials were nausea, vomiting, headache, dizziness, and diarrhea.

Abnormal Hematologic and Clinical Chemistry Findings
See Table 1.

Adverse events with outcome of Death
In a pooled analysis of all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of patients receiving tigecycline and 3.0% (110/3646) of patients receiving comparator drugs. 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 patients. Risk differences in the treatments by infection type are provided in Table 2. The cause of the imbalance has not been established. Generally, deaths were the result of worsening infections or complications of infection or underlying co-morbidities.

Table 2: Patients with Adverse Events with Outcome of Death by Infection Type

	Tigecycline		Comparator		Risk Difference[a]
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[b]	41/336	12.2	42/345	12.2	0.0 (-5.1, 5.2)
VAP[b]	25/131	19.1	15/122	12.3	6.8 (-2.9, 16.2)
MRSA/VRE (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 Adjusted	150/3788	4.0	110/3646	3.0	0.6 (0.1, 1.2) [c]

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI = Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia; MRSA/VRE= Resistant gram-positive pathogen study in patients with MRSA or Vancomycin Resistant Enterococcus (VRE); DFI=diabetic foot infections.

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

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

Infection-related serious adverse events

In Phase 3 clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with tigecycline (6.7%) vs comparators (5.5%). Serious adverse events of sepsis/septic shock were more frequently reported for subjects treated with tigecycline (1.8%) vs comparators (1.2%). Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established (See **WARNINGS AND PRECAUTIONS**). Other events included abscess (1.4% vs 1.2%), infections, including wound infections (1.2% vs 0.9%) and pneumonia (1.1% vs 1.2%) for tigecycline vs comparators, respectively.

Post Marketing Adverse Reactions

The following adverse reactions have been identified during postapproval use of tigecycline: acute pancreatitis including fatal cases, anaphylaxis/anaphylactoid reactions, severe skin reactions including Stevens-Johnson Syndrome and hepatic cholestasis.
There has been one case of ventricular arrhythmia (with positive dechallenge and rechallenge) associated with tigecycline administration.

DRUG INTERACTIONS

Overview

In vitro studies in human liver microsomes indicate that tigecycline does not inhibit metabolism mediated by any of the following 6 cytochrome (CYP) P450 isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. There has been no specific study conducted to examine the effects of tigecycline on microsomal enzyme induction. The exposure and safety data did not show any evidence of increased liver weight during multiple dosing which typically is associated with enzyme induction. 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.

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

Tigecycline (100 mg followed by 50 mg every 12 hours) and digoxin (0.5 mg followed by 0.25 mg every 24 hours) were coadministered 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 pharmacodynamics 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 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.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
There are no reported drug-laboratory test interactions.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Based on pharmacokinetic data in patients with severe hepatic impairment (Child Pugh C), the dose of TIGECYCLINE (tigecycline) should be altered (See **Recommended Dose and Dosage Adjustment**).

Recommended Dose and Dosage Adjustment
The recommended dosage regimen of 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 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 community acquired pneumonia (mild to moderate infections only) 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.

Patients with Hepatic Insufficiency
No dosage adjustment of TIGECYCLINE is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). (See **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

Patients with Severe Hepatic Impairment: Based on the pharmacokinetic profile of tigecycline in patients with severe hepatic impairment (Child Pugh C), the dose of TIGECYCLINE 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 **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

Patients with Renal Insufficiency
Based on the pharmacokinetic data, no dosage adjustment of TIGECYCLINE is necessary in patients with renal impairment or in patients undergoing hemodialysis. (See **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**).

Other
No dosage adjustment of TIGECYCLINE is necessary based on age, gender or race. (See **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

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

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.

Reconstitution:

Parenteral Products:

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
5 mL	5.3 mL	5 mL	10 mg/mL*

*The pH of the reconstituted solution is 4.5 – 5.5.

Each Vial of TIGECYCLINE 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. (Note: Each vial contains a 6% overage. Thus, 5 mL of reconstituted solution is equivalent to 50 mg of the drug.) The vial should be gently swirled until the drug dissolves.

Dilution:

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 two vials; for a 50 mg dose, reconstitute one vial). The maximum concentration in the IV bag should be 1 mg/mL. **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.

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

Once reconstituted, TIGECYCLINE may be stored at room temperature (not to exceed 25°C/77°F) 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 2º to 8ºC (36º to 46ºF) for up to 48 hours following immediate transfer of the reconstituted solution into the IV bag. (See **STORAGE AND STABILITY**).

If the storage conditions exceed 25°C/77°F after reconstitution, tigecycline should be used immediately.

The concentration of the admixture solution is 1 mg/mL (100 mg loading dose/100 mL) or 0.5 mg/mL (50 mg dose in 100 mL).

When administered through a Y-site, TIGECYCLINE, is compatible with the following drugs or diluents when used with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection USP:

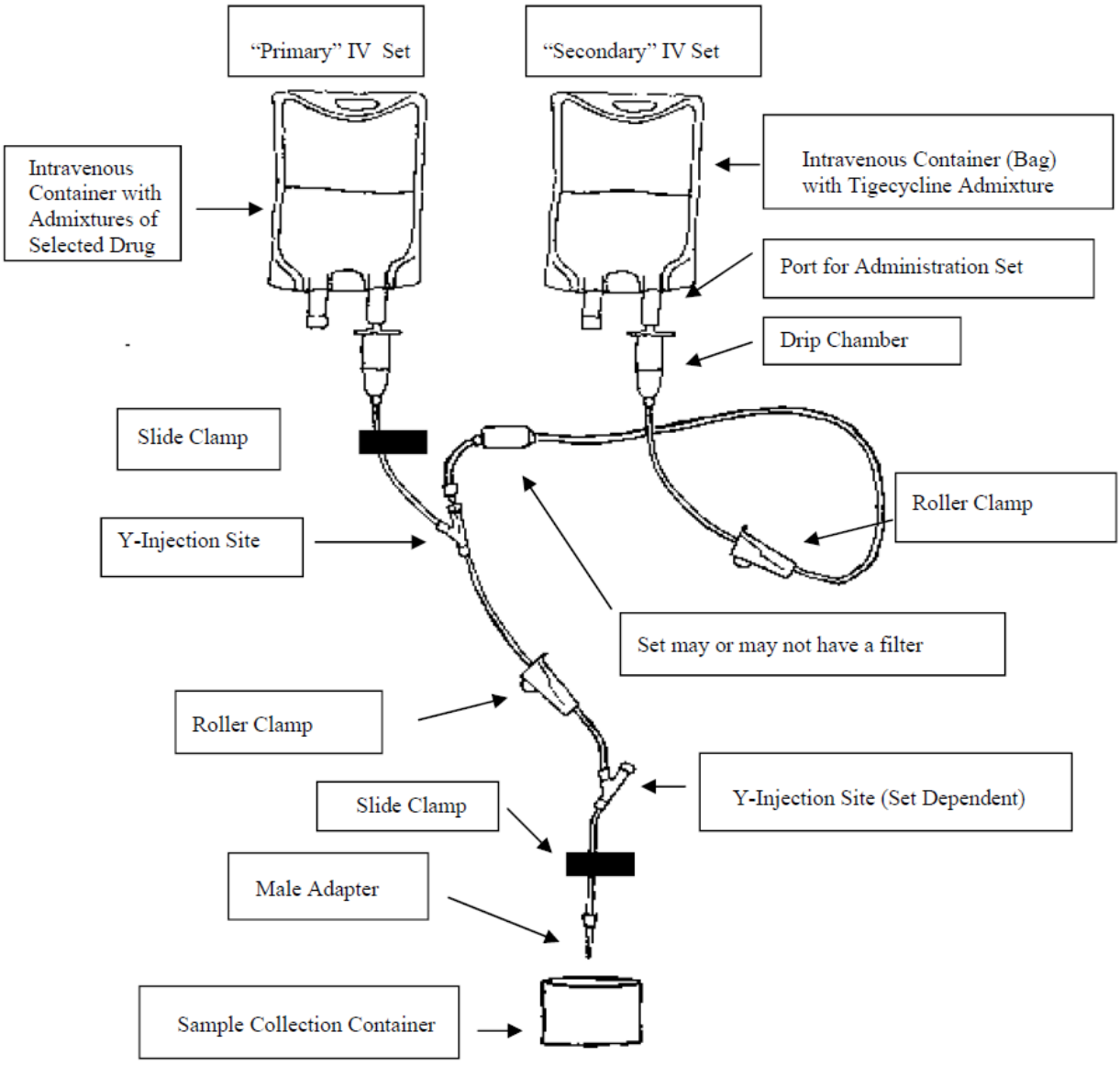
- Dopamine HCl Injection, USP (1.6 mg/mL in 0.9% Sodium Chloride Injection)
- Lidocaine HCl Injection, USP (2.0 mg/mL in 0.9% Sodium Chloride Injection)
- Lactated Ringer's Injection, USP (250 mL bag)
- Potassium Chloride Injection concentrate, USP (0.04 mEq/mL in 0.9% Sodium Chloride Injection)
- Ranitidine Injection, USP (0.6 mg/mL in 0.9% Sodium Chloride Injection)
- Theophylline (1.6 mg/mL in 5% Dextrose Injection)
- Dobutamine Injection, USP (1.0 mg/mL in 0.9% Sodium Chloride Injection)
- Amikacin sulphate Injection, USP (2.5 mg/mL and 5.0 mg/mL in 0.9% Sodium Chloride Injection)
- Gentamicin Injection, USP (1.4 mg/mL in 0.9% Sodium Chloride Injection)
- Tobramycin Injection, USP (1.4 mg/mL in 0.9% Sodium Chloride Injection)
- Haloperidol Injection , USP (0.2 mg/mL in 0.9% Sodium Chloride Injection)
- Metoclopramide Injection, USP (3 mg/mL in 0.9% Sodium Chloride Injection)
- Morphine sulphate Injection, USP (0.5 mg/mL in 0.9% Sodium Chloride Injection)
- Norepinephrine bitartrate Injection, USP (4 µg/mL in 5% Dextrose Injection)
- Propofol Injectable Emulsion 1% (10 mg/mL in 0.9% Sodium Chloride Injection)
- Piperacillin sodium /tazobactam sodium (EDTA formulation) powder for injection

(Piperacillin 40 mg/tazobactam 5 mg/mL in 0.9% Sodium Chloride Injection)

The following drugs should not be administered simultaneously through the same Y-site as TIGECYCLINE: amphotericin B, amphotericin B lipid complex, diazepam, esomeprazole and omeprazole.

A generic schematic diagram for the Y-site co-administration is provided below:

Figure 1: A generic schematic diagram for the Y-site co-administration



OVERDOSAGE

No specific information is available on the treatment of overdosage with TIGECYCLINE (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.

For the management of suspected drug overdose, contact your regional Poison Control Centre**.**

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Tigecycline, a glycylcycline, acts by inhibiting protein synthesis at the level of the bacterial ribosome by blocking the binding of amino-acyl tRNA to the A site of the ribosome. Tigecycline has *in vivo* and *in vitro* antibacterial activity against a broad-spectrum of pathogens. (see **MICROBIOLOGY**). Tigecycline is active against bacterial strains that carry classical tetracycline resistant genes encoding either ribosomal protection or a tetracycline efflux pump. Several efflux-related resistance mechanisms have been identified that provide decreased activity (*Proteus* spp., *Providencia* spp., & *Morganella* spp.) or no activity (*P. aeruginosa* spp.).

Pharmacokinetics

The mean pharmacokinetic parameters of tigecycline after single and multiple intravenous doses are summarized in Table 3. Intravenous infusions of tigecycline were administered over approximately 30 to 60 minutes.

Table 3: Mean (CV%) Pharmacokinetic Parameters of Tigecycline

	Single Doses	Multiple Doses[a]
	100 mg	50 mg q12h
C_{max} (µg/mL)[b]	1.45 (22%)	0.87 (27%)
C_{max} (µg/mL)[c]	0.90 (30%)	0.63 (15%)
AUC (µg.hr/mL)	5.19 (36%)	- -
$AUC_{0\text{-}24h}$ (µg.hr/mL)	- -	4.70 (36%)
C_{min} (µg/mL)	- -	0.13 (59%)
$t_{1/2}$ (hr)	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] 100 mg initially, followed by 50 mg every 12 hours
[b] 30-minute infusion
[c] 60-minute infusion

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 ^{14}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·hr/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·hr/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 (8.6-fold, n=1), and colon (2.1-fold, n=5). 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.

Excretion: 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.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of tigecycline in patients less than 18 years of age have not been established. (See **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

Geriatrics: 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. (See **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

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 (22.8±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.

Hepatic Insufficiency: In a study comparing 10 patients with mild hepatic impairment (Child-Pugh A), 10 patients with moderate hepatic impairment (Child-Pugh B), and 5 patients with severe hepatic impairment to 23 age and weight matched healthy control subjects, the single-dose pharmacokinetic disposition of tigecycline was not altered in patients with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25% and the half-life of tigecycline was prolonged by 23% in patients with moderate hepatic impairment (Child-Pugh B). In addition, systemic clearance of tigecycline was reduced by 55%, and the half-life of tigecycline is prolonged by 43% in patients with severe hepatic impairment (Child-Pugh C). Based on the pharmacokinetic profile of tigecycline, no dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). However, in patients with severe hepatic impairment (Child Pugh C), the dose of tigecycline should be reduced 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 **DOSAGE AND ADMINISTRATION, Patients with Severe Hepatic Impairment**).

Renal Insufficiency: A single dose study compared 6 subjects with severe renal impairment (creatinine clearance $\leq$30 mL/min), 4 end stage renal disease patients receiving tigecycline 2 hours before hemodialysis, 4 end stage renal disease patients receiving tigecycline after hemodialysis, and 6 healthy control subjects. The pharmacokinetic profile of tigecycline was not altered in any of the renally impaired patient groups nor was tigecycline removed by hemodialysis. No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing hemodialysis. (See **DOSAGE AND ADMINISTRATION**).

Cardiovascular: In a phase 2 study, ECG results are available from 88 subjects treated with tigecycline. Median change from baseline for QT corrected using the Fridericia formula (QTc(F)) and using a log-linear method (QTc(L)) were 8.5 msec and -4.9 msec, respectively. The upper bounds of a 2-sided 95% confidence interval (CI) were 14.0 and 0.6 msec, respectively. No apparent clinically important effects on cardiac repolarization were seen in subjects treated with tigecycline in this trial. Categorical analyses of QTc(F) and QTc(L) changes $\geq$ 60 msec from baseline occurred in 6.8% and 1.1% of the subjects, respectively. However, interpretation of these results is limited because of the relatively small sample size and lack of a control group in this trial.

The results from phase 3 studies involving ECGs from 773 subjects showed that the median changes from baseline for QTc(F) and QTc(L) were 6.0 and 3.3 msec, respectively, with an upper bound of a 2-sided 95% CI of 7 and 5 msec, respectively. Comparable median change values from subjects treated with comparator agents (n=788) were 3.0 and 1.2 msec, with upper bounds of the 95% CI of 5 and 3 msec, respectively. Categorical analyses of QTc(F) and QTc(L) changes $\geq$ 60 msec from baseline occurred, respectively, in 1.8% and 1.3% of tigecycline-treated subjects and in 0.8% and 0.6% of comparator subjects. The differences between the tigecycline and comparator groups were statistically significant for the QTc(F)

analysis. QTc(F) and QTc(L) absolute values > 500 msec occurred in 0.4% of tigecycline-treated subjects and in none of the comparator subjects. These differences between the tigecycline and comparator groups were not statistically significant. Although an effect on cardiac repolarization following administration of tigecycline cannot be absolutely excluded, the overall median changes from baseline in the phase 3 studies were generally small, with the upper bounds of the 95% CI $\leq$10 msec, without associated drug-related adverse cardiac events being reported in concert with any significant changes in QTc.

STORAGE AND STABILITY

Prior to reconstitution, TIGECYCLINE lyophilized powder should be stored at a controlled room temperature 20º-25ºC (68º-77ºF), excursions permitted to 15º-30ºC (59º-86ºF) for up to the expiration date specified on the label. Once reconstituted, TIGECYCLINE may be stored at room temperature (not to exceed 25°C/77°F) 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, 5% Dextrose Injection USP may be stored refrigerated at 2º to 8ºC (36º to 46ºF) for up to 48 hours following immediate transfer of the reconstituted solution into the IV bag.

If the storage conditions exceed 25°C/77°F after reconstitution, tigecycline should be used immediately.

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms:
TIGECYCLINE (tigecycline) for injection is supplied in a single-dose 5 mL Type I glass vial.

TIGECYCLINE is an orange lyophilized powder or cake. Each TIGECYCLINE vial contains 50 mg tigecycline lyophilized powder for intravenous infusion and 100 mg of lactose monohydrate. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide. The product does not contain preservatives.

Supplied 10 vials per box.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

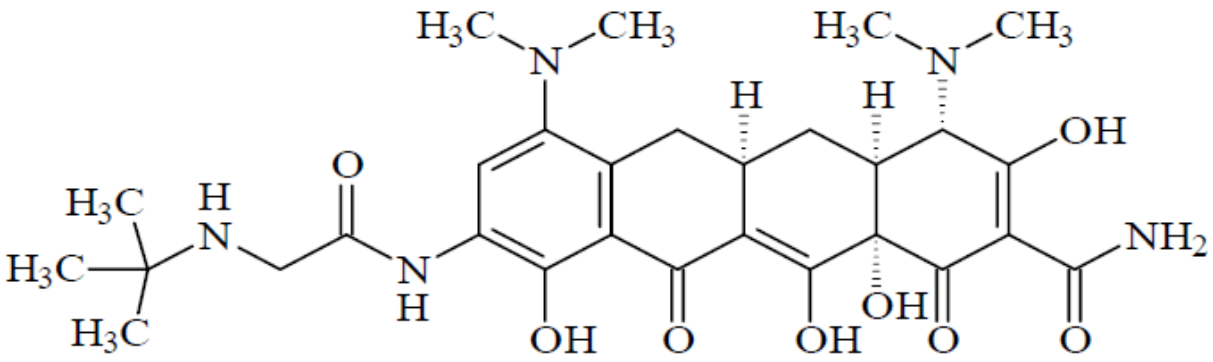
Drug Substance

Common name: Tigecycline

Chemical name: (4*S*,4aS,5aR,12aS)-9-[2-(*tert*-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12atetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

Molecular formula and molecular mass: $C_{29}H_{39}N_5\,N_5O_8$ (585.65)

Structural formula:



Physicochemical properties: Tigecycline is an orange powder. The reconstituted solution is yellow to orange, essentially free of particulate matter. Tigecycline is highly ionic and freely soluble throughout the entire pH range of 1 to 14.

pH: The pH of a 1% aqueous solution of Tigecycline is 7.7 – 8.2.

Melting Range: Under hot stage microscopic examination, Tigecycline melts at 165ºC – 175ºC to form a yellow liquid, which decomposes upon further heating to 185°C.

Partition Coefficient: The n-Octanol/water partition coefficient is 1.338 at pH 8.

CLINICAL TRIALS

Complicated Skin and Skin Structure Infections

Tigecycline was studied for the treatment of complicated skin and skin structure Infections (cSSSI) in 2 clinical trials.

Patients with complicated deep soft tissue infection including cellulitis (> 10 cm, requiring surgery/drainage or with complicated underlying disease), wound infections, major abscesses, infected ulcers, and burns were enrolled. Patients with severe underlying disease, such as those who were immunocompromised, patients with decubitus ulcer infections, or patients who had infections requiring longer than 14 days of treatment (for example, necrotizing fasciitis), were not enrolled.

Table 4: Phase 3 Clinical Studies for cSSSI – Study Demographics and Trial Design

Study No.	Study Design	No. of Subjects Randomized	Demography: Sex, Age Range (Mean Age),	IV Dose and Frequency (Duration of Treatment)
3074A1-300-US/CA	Double-blind (third-party unblinded), randomized control comparison study of tigecycline + placebo and vancomycin + aztreonam to treat cSSSI	583	368 M, 205 W 18–92 years (48.9 years)	Tigecycline Arm: 100 mg loading, 50 mg maintenance every 12 hours over 60 minutes (5–14 days) Vancomycin + aztreonam Arm: 1 g vancomycin + 2 g aztreonam every 12 hours (5–14 days)
3074A1-305-WW	Double-blind (third-party unblinded), randomized control comparison study of tigecycline + placebo and vancomycin + aztreonam to treat cSSSI	546	330 M, 213 W 18–88 years (49.4 years)	Tigecycline Arm: 100 mg loading, 50 mg maintenance every 12 hours over 60 minutes (5–14 days) Vancomycin + aztreonam Arm: 1 g vancomycin + 2 g aztreonam every 12 hours (5–14 days)

The primary efficacy endpoint was the clinical response at the test of cure (TOC window for the final analyses was 12 to 92 days post therapy) visit in the co-primary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) patients. See Table 5. Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 6.

Table 5: Clinical Cure[b] Rates in Complicated Skin and Skin Structure Infection

	Tigecycline n / N (%)	Comparator n / N (%)	95% CI [a]
Integrated			
CE	365/422 (86.5)	364/411 (88.6)	-6.8, 2.7
c-mITT	429/538 (79.7)	425/519 (81.9)	-7.1, 2.8
Study 300			
CE	165/199 (82.9)	163/198 (82.3)	-7.4, 8.6
c-mITT	209/277 (75.5)	200/260 (76.9)	-9.0, 6.1
Study 305			
CE	200/223 (89.7)	201/213 (94.4)	-10.2, 0.8
c-mITT	220/261 (84.3)	225/259 (86.9)	-9.0, 3.8

[a.] Confidence Interval (95% CI) were calculated from a generalized linear model with a binomial probability function and an identity link

[b.] The patient had resolution of all signs and symptoms of the infection (healing of chronic underlying skin ulcer was not required) or improvement to such an extent that no further antibacterial therapy was necessary.

Table 6: Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Complicated Skin and Skin Structure Infections[a]

Pathogen	Tigecycline n / N (%)	Comparator n / N (%)
Escherichia coli	25/29 (86.2)	26/30 (86.7)
Enterobacter cloacae	7/9 (77.8)	14/14 (100)
Enterococcus faecalis (vancomycin-susceptible only)	12/16 (75.0)	19/24 (79.2)
Klebsiella pneumoniae	8/9 (88.9)	15/16 (93.8)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	123/135 (91.1)	113/120 (94.2)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	29/37 (78.4)	26/34 (76.5)
Streptococcus agalactiae	8/8 (100)	11/13 (84.6)
Streptococcus anginosus.	16/20 (80.0)	9/10 (90.0)
Streptococcus pyogenes	31/32 (96.9)	24/27 (88.9)
Bacteroides fragilis	6/8 (75.0)	4/5 (80.0)

a. Two cSSSI pivotal studies

Complicated Intra-abdominal Infections

Tigecycline was studied for the treatment of complicated intra-abdominal infections (cIAI) in 2 clinical trials.

Patients with complicated diagnoses including appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis were enrolled.

Table 7: Phase 3 Clinical Studies for cIAI – Study Demographics and Trial Design

Study No.	Study Design	No. of Subjects Randomized	Demography: Sex, Age Range (Mean Age),	IV Dose and Frequency (Duration of Treatment)
3074A1-301-WW	Double-blind (third-party unblinded), randomized control comparison study of tigecycline and imipenem/cilastatin to treat cIAI	834	537 M, 288 W 18–91 years (43.6 years)	Tigecycline Arm: 100 mg loading, 50 mg maintenance every 12 hours over 30 minutes (5–14 days) Imipenem/Cilastatin Arm: 500 mg every 6 hours (5-14 days)
3074A1-306-WW	Double-blind (third-party unblinded), randomized control comparison study of tigecycline and imipenem/cilastatin to treat cIAI	824	479 M, 338 W 18–88 years (48.9 years)	Tigecycline Arm: 100 mg loading, 50 mg maintenance every 12 hours over 30 minutes (5–14 days) Imipenem/Cilastatin Arm: 500 mg every 6 hours (5-14 days)

The primary efficacy endpoint was the clinical response at the TOC visit (Test of Cure window for the final analyses was 12 to 44 days post therapy) for the co-primary populations of the microbiologically evaluable (ME) and the microbiologic modified intent to treat (m-mITT) patients. See Table 8. Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 9.

Table 8: Clinical Cure[b] Rates in Complicated Intra-Abdominal Infection

	Tigecycline n / N (%)	Comparator n / N (%)	95% CI [a]
Integrated			
ME	441/512 (86.1)	442/513 (86.2)	-4.5, 4.4
m-mITT	506/631 (80.2)	514/631 (81.5)	-5.8, 3.2
Study 301			
ME	199/247 (80.6)	210/255 (82.4)	-9.0, 5.4
m-mITT	227/309 (73.5)	244/312 (78.2)	-11.8, 2.3
Study 306			
ME	242/265 (91.3)	232/258 (89.9)	-4.0, 6.8
m-mITT	279/322 (86.6)	270/319 (84.6)	-3.7, 7.7

[a.] Confidence Interval (95% CI) were calculated from a generalized linear model with a binomial probability function and an identity link

[b.] The test article and initial intervention (operative and/or radiologically controlled drainage procedure) resolved the intra-abdominal infection. If the patient underwent a percutaneous drainage at baseline, did not respond to treatment within 72 hours of the initial drainage, and underwent an operation and then improved he/she was considered a clinical cure. The patient must not have received additional antibacterial agents during treatment.

Table 9: Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Complicated Intra-Abdominal Infections[a]

Pathogen	Tigecycline n / N (%)	Comparator n / N (%)
Citrobacter freundii	12/16 (75.0)	3/4 (75.0)
Enterobacter cloacae	14/16 (87.5)	16/17 (94.1)
Escherichia coli	281/329 (85.4)	298/343 (86.9)
Klebsiella oxytoca	19/20 (95.0)	18/20 (90.0)
Klebsiella pneumoniae	46/52 (88.5)	53/60 (88.3)
Enterococcus faecalis (vancomycin susceptible only)	25/33 (75.8)	35/47 (74.5)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	26/29 (89.7)	22/24 (91.7)
Streptococcus anginosus grp[b]	102/120 (85.0)	61/81 (75.3)
Bacteroides fragilis	67/87 (77.0)	60/74 (81.1)
Bacteroides thetaiotaomicron	36/41 (87.8)	31/36 (86.1)
Bacteroides uniformis	12/17 (70.6)	14/17 (82.4)
Bacteroides vulgatus	14/16 (87.5)	5/7 (71.4)
Clostridium perfringens	19/20 (95.0)	20/22 (90.9)
Peptostreptococcus micros	14/18 (77.8)	9/12 (75.0)

a. Two cIAI pivotal studies
b. Includes *Streptococcus anginosus, Streptococcus intermedius, and Streptococcus constellatus*

Community Acquired Pneumonia (mild to moderate infections only)

Tigecycline was studied for the treatment of community acquired pneumonia (mild to moderate infections only) (CAP) in 2 clinical trials.

Patients (18 years of age or older) with community acquired pneumonia who required hospitalization and IV therapy were enrolled in the studies. Patients who required treatment in an intensive care unit, were immunocompromised, or were hospitalized within the 14 days prior to the onset of symptoms or resided in a long-term care facility or nursing home ≥14 days before the onset of symptoms were not enrolled in the studies.

In clinical trials in patients with community-acquired pneumonia who required hospitalization and who received at least 1 dose of tigecycline, 20 % had Fine Pneumonia Severity Index scores ≥ IV. Two (2) tigecycline treated patients had a Fine Pneumonia Severity Index score of V. Underlying cardiopulmonary conditions included chronic obstructive pulmonary disease (COPD) in 12 % of patients and congestive heart failure in 7 %. Multilobar disease was noted in 25 % of

patients, bilateral disease in 17 %, and pleural effusions in 7 %. *S. pneumoniae* bacteremia was documented in 6 % of patients.

Table 10: Phase 3 Clinical Studies for CAP – Study Demographics and Trial Design

Study No.	Study Design	No. of Subjects Randomized	Demography: Sex, Age Range (Mean Age),	IV Dose and Frequency (Duration of Treatment)
3074A1-308-WW	Double-blind (third-party unblinded), randomized active control comparison study of tigecycline and levofloxacin to treat CAP	418	244M, 174 W 18-91years (55 years)	Tigecycline Arm: 100 mg loading, 50 mg maintenance every 12 hours over 30 minutes (7–14 days) Levofloxacin Arm: 500 mg levofloxacin every 24 hours (7-14 days) Switch to oral levofloxacin (500 mg every day) was permitted for both arms after at least 3 days of IV therapy was administered (in-patient)
3074A1-313-WW	Double-blind (third-party unblinded), randomized active control comparison study of tigecycline and levofloxacin to treat CAP	428	264 M, 164 W 17-92 years (50 years)	Tigecycline Arm: 100 mg loading, 50 mg maintenance every 12 hours over 30 minutes (7–14 days) Levofloxacin Arm: 500 mg levofloxacin IV every 12 or 24 hours (7-14 days)

The primary efficacy endpoint was the clinical response at the test of cure (TOC window for the final analyses was 7-23 days post therapy) visit in the co-primary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) patients. See Table 11. Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 12.

Table 11: Clinical Cure[b] Rates in Community Acquired Pneumonia[c]

	Tigecycline n/N (%)	Comparator n/N (%)	95% CI [a]
Integrated			
CE	253/282 (89.7)	252/292 (86.3)	-2.2, 9.1
c-mITT	319/394 (81.0)	321/403 (79.7)	-4.5, 7.1
Study 308			

CE	125/138 (90.6)	136/156 (87.2)	-4.4, 11.2
c-mITT	149/191 (78.0)	158/203 (77.8)	-8.5, 8.9
Study 313			
CE	128/144 (88.9)	116/136 (85.3)	-5.0, 12.2
c-mITT	170/203 (83.7)	163/200 (81.5)	-5.6, 10.1

[a.] Confidence Interval (95% CI) were calculated from a generalized linear main-effects model including Fine category with a binomial probability function and an identity link.

[b.] All signs and symptoms of the pneumonia present at the time of enrollment were improved or resolved at TOC.
Chest radiographs were improved or no worse. No further antibiotic therapy was necessary for treatment of pneumonia. There was no worsening or appearance of new signs and symptoms of pneumonia.

[c.] Tigecycline is not indicated for severe CAP.

Table 12: Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Community Acquired Pneumonia[a]

Pathogen	Tigecycline n/N (%)	Comparator n/N (%)
Haemophilus influenzae	14/17 (82.4)	13/16 (81.3)
Streptococcus pneumoniae (penicillin-susceptible only)	44/46 (95.7)	39/44 (88.6)
Mycoplasma pneumoniae	37/39 (94.9)	44/48 (91.7)
Chlamydia pneumoniae	18/19 (94.7)	26/27 (96.3)

[a.] Two CAP pivotal studies

DETAILED PHARMACOLOGY

Animal Pharmacology
In Vivo
Pharmacokinetics

Tigecycline is not absorbed systemically after oral administration in rats and monkeys. The intravenous single dose pharmacokinetics of tigecycline in rats and dogs was characterized by CL_T of 2.70 and 0.369 L/h/kg, an apparent Vdss of 3.43 and 3.08 L/kg, and elimination $t_{1/2}$ values of 1-4 and 8 hours, respectively. In rats, rabbits, and dogs, exposures increased with dose over a dose range of 0.2 to 70 mg/kg/day. In rats and rabbits, $C_{5\ min}$ and AUC increased in a greater than dose proportional manner. In rats, CL_T and Vdss decreased with increasing dose. Repeat, daily IV administration of tigecycline to rats and dogs for 13 weeks resulted in increases in AUC values of 1.24 to 2.45 fold compared with AUC values after a single dose. No sex-related differences in pharmacokinetics were observed.

The tissue distribution of [^{14}C] Tigecycline-derived radioactivity was evaluated in rats and is summarized in Table 13.

Table 13: Tissue Distribution of Total Radioactivity in Rats After IV Bolus Administration of 3 mg/kg [^{14}C]Tigecycline for 10 Days[b]

Tissues/Organs	C_{max} (µg eq/g)	AUC_{0-336} (µg eq • h/g)	R (Accumulation Ratio) [c]
Blood	2.17[a]	13.8	1.2
Bone	16.7	3938	6.7
Bone Marrow[d]	9.34	181	1.4
Epididymides	1.25	15.3	1.1
Kidney	9.99	108	1.4
Liver	10.3	~50.7	1.4
Lymph Nodes[d,e]	3.36	31.8	1.4
Plasma	2.04[a]	6.63	1.1
Prostate	3.34	33.1	1.2
Salivary	5.57	80.3	1.2
Skin	2.92	72.5	2.9
Spleen [d,e]	8.25	67.5	1.4
Thyroid	5.55	375	2.6

a. $C_{5\ min}$ values
b. data from day 10 by method of quantitative tissue dissection, unless otherwise noted
c. a ratio of day 10 AUC to day 1 AUC, unless otherwise noted
d. data from day 6
e. data by method of quantitative whole body autoradiography

Plasma protein binding ranged from 72% to 92% over tigecycline concentrations of 0.1 to 15 ug/mL in the mouse, rat, dog and rabbit.

The placental transfer of [^{14}C]tigecycline after single IV administration to gravid rats (3 mg/kg) on gestation day (GD) 17 was evaluated. Radioactivity was rapidly distributed into the placenta, fetus, and amniotic fluid. Radioactivity was specifically retained in fetal bone and ossification sites. Exposure to the fetus was approximately 1.5 times greater than maternal serum (See Table 14). Radioactivity was excreted readily into the milk of lactating rats on post-partum day 14; however, little radioactivity was detected in the serum of nursing pups.

The metabolism of IV administered tigecycline was evaluated in rats and dogs. Unchanged tigecycline was the predominant form in plasma and urine of rats and dogs (≥ 80% of sample radioactivity in the first 6 or 8 hours post-dose). The degradation product, 4-epimer of tigecycline, was observed in plasma and urine of both the rat and dog (< 10% of sample radioactivity up to 6 or 8 hours post-dose). The metabolism of tigecycline was not characterized in mice, guinea pigs, rabbits, or monkeys. Humans metabolized tigecycline to a glucuronide metabolite, which accounted for up to 15.3% of circulating radioactivity and 9.6% of the administered dose, and an N-acetyl 9-aminominocycline metabolite, which represented up to 11.3% relative to concurrent tigecycline concentrations and accounted for 3% of administered dose. The glucuronide and N-acetyl 9-aminominocycline metabolites were not observed in animals used for toxicity studies.

Table 14: Distribution of Total Radioactivity in Pregnant Rats After IV Administration of 3 mg/kg [^{14}C] Tigecycline[a] – Quantitative Tissue Dissection

Tissues/Organs	C_{max} (µg eq/g)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (µg eq•h/g)	Tissue: Serum $AUC_{0-\infty}$
Amniotic Fluid	0.108	0.5	21.5	2.50	0.5
Blood[b]	2.48	0	17.5	6.41	1.2
Bone	2.17	0.5	ND	60.7[c]	12.0[c]
Fetus	0.291	0.5	21.7	7.64	1.5
Placenta	1.38	0.5	19.8	17.0	3.2
Serum	2.55	0	17.9	5.26	1.0

a. single dose, bolus administration on gestation day 17
b. $C_{5\ min}$ values
c. AUC_{0-72}

Central Nervous and Respiratory Systems

Rats were administered a single, IV, bolus dose of tigecycline at dosages of 0, 5, 15, or 30 mg/kg and were evaluated over a 24-hour period for effects on the CNS and on the respiratory system (respiratory rate, tidal volume and minute volume). Administration of tigecycline did not elicit any toxicologically significant effects on the CNS or respiratory system in rats at the dosages administered.

The effect of tigecycline on thiopental-induced sleep time was evaluated in a pharmacology study. In this study, Institute for Cancer Research (ICR) mice were administered an IV dosage of 35 mg/kg of thiopental sodium followed by an intravenous (IV) bolus administration of 3, 10, or 30 mg/kg of tigecycline. A dosage of 3 mg/kg of tigecycline did not produce mortality and had no influence on sleeping time induced by thiopental sodium. At dosages of 10 and 30 mg/kg, bolus IV tigecycline induced death in thiopental treated mice and prolonged the sleeping time of surviving mice. At 30 mg/kg, more than 50 % of animals died in this study. In an acute toxicity study, the estimated median lethal dosage [LD_{50}] of tigecycline was 124 and 98 mg/kg in male and female mice, respectively. The lethality induced by coadministration of tigecycline and thiopental was prevented by pretreatment with histamine antagonists (diphenhydramine hydrochloride 5 mg/kg IV and cimetidine 5 mg/kg IV). However, the prolongation of thiopental-induced sleeping time observed after tigecycline coadministration was not inhibited by histamine antagonists. Histamine-induced alterations in sleep time are mediated by H3 receptors, and would not be expected to be altered by diphenhydramine or cimetidine. The basis for the combination of thiopental and tigecycline lowering the lethal dosage of tigecycline is not known, but appears to be due to an interaction between the effects of histamine and thiopental. The administration of tigecycline has been associated with histamine release, based on clinical signs (eg, periorbital swelling, lacrimation, red discoloration around mouth and/or eyes, salivation, edema, decreased activity, soft feces in rats at dosages $\geq$ 20 mg/kg/day and/or dogs at dosages $\geq$ 5 mg/kg/day) or direct measurement of histamine levels (in dogs), and one of the effects of increased histamine levels is to decrease blood pressure. Blood pressure is also reduced following the administration of an anesthetic dose of thiopental. Furthermore, the intraventricular injection of histamine has also been shown to increase thiopental-induced sleep time in mice by approximately 30% to 78% following the administration of 0.5 to 10 µg. Thus, tigecycline and thiopental together may have an additive or synergistic effect and decrease blood pressure to a point beyond which the animal cannot recover.

Cardiovascular System

The effects of IV administration of tigecycline on the cardiovascular system were evaluated in rats and dogs. Rats were administered 0, 5, or 25 mg/kg tigecycline as a single 1-hour IV infusion. There were no tigecycline-related effects on mean arterial blood pressure, heart rate, or spontaneous gross motor activity.

Dogs were administered tigecycline by a single 30-minute IV infusion at dosages of 0, 2, 5, and 12 mg/kg using an escalating-dose design. Arterial blood pressure (systolic, diastolic, and mean), heart rate, electrocardiogram (ECG), and spontaneous gross motor activity were monitored by telemetry every 30 minutes for 24 hours before and after dosing. There were no tigecycline-related effects on ECG, including QT interval, at any dosage. At 12 mg/kg, a transient increase in heart rate and spontaneous motor activity, and a transient increase in mean arterial blood pressure followed by a decrease in blood pressure were observed. These cardiovascular effects in dogs were likely the result of histamine release induced by the IV administration of the high dosage of tigecycline (12 mg/kg), since clinical observations consistent with a histamine reaction were typically observed in rats and dogs in the toxicology studies where high IV dosages were explored.

Other Systems

A variety of *in vitro* and *in vivo* pharmacology studies were conducted with tigecycline to assess pharmacologic effects on the following: general activity and behavior, the autonomic nervous system, smooth muscle and the digestive system in mice; body temperature in mice and rats; water and electrolyte balance in rats; bronchoresistance, heart rate, and blood pressure in guinea pigs; the respiratory and cardiovascular systems in rabbits; contractility of isolated guinea pig ileum; and histamine release from isolated human leukocytes.
In general, tigecycline as IV infusion had no untoward pharmacologic effects in these studies at clinically relevant dosages. The findings from these studies were consistent with the results from the more detailed safety pharmacology and toxicology studies performed with tigecycline and reviewed elsewhere in this overview.

The monohydrochloride salt of tigecycline was evaluated in the Novascreen general side effect profile assay. No significant activity (results within baseline range) was observed in 34 diverse biological assays at concentrations of 1.0^{-9}, 1.0^{-7}, and 1.0^{-5} M.

Human Pharmacology

In Vivo
Pharmacokinetics

Table 15: Clinical Pharmacology and Biopharmaceutics Studies

Study	Dose (n Analyzed)	Enrolled/Analyzed (Sex/Race)	Results and Conclusions
Double-blind, placebo-controlled ascending single-dose study to assess safety, tolerability, and PK of tigecycline (3074A1-100-EU, CSR-35495)	1-hour infusions 12.5 mg (n=6) 25 mg (n=6) 50 mg (n=6) 75 mg (n=6) 100 mg (n=6) 200 mg (n=6)	90/90 (90M/89W, 1O)	Tigecycline exhibited linear pharmacokinetics in the dose ranges studied (12.5 to 300 mg). Tigecycline is well distributed into tissues with a large V_{ss} (7 to 14 L/kg) and was eliminated slowly with a long $t_{1/2}$ ($\geq$40 h). Less than

Study	Dose (n Analyzed)	Enrolled/Analyzed (Sex/Race)	Results and Conclusions
	200 mg fed (n=6) 200 mg + antiemetic (n=6) 300 mg (n=6) 4-hour infusions 200 mg (n=6) 300 mg (n=6)		13% of the tigecycline dose was excreted in urine as unchanged drug. Also, food does not affect the pharmacokinetics of IV tigecycline. The maximum tolerated dose in healthy subjects was 100 mg for fasting administration and 200 mg for postprandial administration.
Double-blind, placebo-controlled ascending single-dose study to assess safety, tolerability, and PK of tigecycline in Chinese subjects (3074A1-106-CN, CSR-54367)	0.5-hour infusion 25 mg (n=8) 50 mg (n=8) 75 mg (n=8) 100 mg (n=8)	48/48 (48M/48A)	Tigecycline exhibited linear pharmacokinetics in the dose range studied (25 to 100 mg) with a large V_{ss}, low systemic clearance, and a relatively long $t_{1/2}$. The pharmacokinetic profile of tigecycline in this study in Chinese men is similar to the pharmacokinetic profile in a previous study in non-Chinese men. The administration of single 25- to 150-mg IV doses of tigecycline was generally safe and well tolerated in healthy Chinese men.
Double-blind, placebo-controlled ascending single-dose study to assess safety, tolerability, and PK of tigecycline in Japanese subjects (3074A1-107-JA, CSR-54680)	1-hour infusions 25 mg (n=8) 50 mg (n=8) 100 mg (n=8) 150 mg (n=8)	40/40 (40M/40A)	Due to limitations of the drug assay, tigecycline $t_{1/2}$ and V_{ss} appeared to increase at higher doses, and the clearance appeared to decrease at higher doses. Approximately 14% to 17% of the dose was recovered in urine as unchanged tigecycline. The pharmacokinetic profile of tigecycline in this study in Japanese men is similar to the pharmacokinetic profile in a previous study in non-Japanese men.
Double-blind, placebo-controlled ascending multiple-dose study to assess safety, tolerability, and PK of tigecycline (3074A1-101-US, CSR-39534)	1-hour infusions 25 mg q12h (n=6) 50 mg q12h (n=6) 75 mg q12h (n=6) 100 mg q12h (n=6)	32/32 (32M/11B, 4H, 17W)	Tigecycline exhibited linear pharmacokinetics in the dose range studied (25 mg q12h to 100 mg q12h). Tigecycline has a long $t_{1/2}$ and a high V_{ss}, indicating extensive tissue distribution. The maximum tolerated repeated dose in healthy subjects was 50 mg q12h.
Open-label, nonrandomized, multiple-dose mass balance and metabolic	0.5-hour infusions 100 mg + 50 mg q12h (n=12) followed by	12/12 (12M/2B, 10W)	Tigecycline is the major drug-related component in serum, urine, and feces. The recovery of total radioactivity in feces and urine

Study	Dose (n Analyzed)	Enrolled/Analyzed (Sex/Race)	Results and Conclusions
disposition of ^{14}C-tigecycline (3074A1-104-US, CSR-52364)	^{14}C-tigecycline 50 mg (n=6)		indicates that the majority (59%) of the dose is eliminated by biliary/fecal excretion, and a smaller amount (33%) is excreted in urine. The primary elimination pathway of tigecycline is biliary excretion of unchanged tigecycline. The secondary elimination pathways of tigecycline are renal excretion of unchanged tigecycline, glucuronidation, and metabolism to N-acetyl-9-aminominocycline, and these secondary pathways each account for ≤15% of the total elimination of tigecycline.
Open-label, nonrandomized, multiple-dose evaluation of PK in epithelial lining fluid (ELF) and alveolar cells (AC) following bronchoalveolar lavage (3074A1-112-US, CSR-53846)	0.5-hour infusions 100 mg + 50 mg q12h (n=33)	34/34 (9F, 25M/3A, 4B, 27W)	Tigecycline partitions slowly into AC (t_{max} = 2 h) and more slowly into ELF (t_{max} = 6 h). Tigecycline exhibited good penetration into the AC and ELF. The ELF AUC was 1.3-fold higher than serum, and AC AUC was 77.5-fold higher than serum. At all times, tigecycline concentrations in AC were more than 20-fold higher than the MIC_{90}s of common pathogens that cause pneumonia.
Open-label, nonrandomized, multiple-dose evaluation of PK in cantharidin-induced skin blister fluid (3074A1-113-US, CSR-53610)	0.5-hour infusions 100 mg + 50 mg q12h (n=10)	10/10 (10M/1B, 2O, 7W)	Tigecycline partitions slowly into skin blister fluid (t_{max} = 2.8 h). The ratio of blister fluid AUC to serum AUC was 74%, indicating that tigecycline exhibits good penetration into the skin.
Open-label, nonrandomized, single-dose evaluation of PK in tissues (bone, bile, colon, gallbladder, lung, synovial fluid) from subjects undergoing elective surgery or procedure for tissue removal (3074A1-117-US, CSR-53852)	0.5-hour infusions 100 mg (n=54)	54/54 (36F, 18M/1B, 3O, 50W)	At 4 hours after a single dose of tigecycline 100 mg, tissue concentrations in gall bladder, lung, and colon, were 38-fold, 8.6-fold, and 2.1-fold higher than the concentrations in serum, respectively, indicating that tigecycline achieves concentrations at or above the MICs that are expected to be active against a broad range of pathogens in these tissues.
Open-label,	1-hour infusions of	46/46	The pharmacokinetics and the

Study	Dose (n Analyzed)	Enrolled/Analyzed (Sex/Race)	Results and Conclusions
nonrandomized, single-dose evaluation of PK in young and elderly men and women (3074A1-102-US, CSR-41557)	100 mg M 18-50 years (n=9) F 18-50 years (n=8) M 65-75 years (n=8) F 65-75 years (n=7) M >75 years (n=8) F >75 years (n=5)	(21F, 25M/14B, 2H, 30W)	tolerability of tigecycline were not markedly different between men and women of the same age group or across various age groups. From a pharmacokinetic point of view, dosage adjustments are not necessary based upon age or sex.
Open-label, nonrandomized, single-dose evaluation of PK in healthy subjects and subjects with severe renal impairment (3074A1-103-US, CSR-43752)	1-hour infusions of 100 mg healthy (n=6) severe impairment (n=6) ESRD predialysis (n=4) ESRD postdialysis (n=4)	20/20 (5F, 15M/11B, 9W)	The systemic clearance of tigecycline was reduced by approximately 20% in subjects with severe renal impairment or end-stage renal disease (ESRD), and tigecycline AUC increased by approximately 30% in these subjects. Additionally, hemodialysis did not remove tigecycline from the systemic circulation. The tigecycline dose does not need to be adjusted in subjects with renal impairment, including subjects with ESRD.
Open-label, nonrandomized, single-dose evaluation of PK in healthy subjects and subjects with hepatic impairment (3074A1-105-EU, CSR-53265)	1-hour infusions of 100 mg healthy (n=23) Child Pugh A (n=10) Child Pugh B (n=10) Child Pugh C (n=5)	48/48 (8F, 40M/4A, 1B, 43W)	The tigecycline clearance in Child Pugh A subjects was similar to that of the healthy subjects, but the clearance in Child Pugh B and Child Pugh C subjects was approximately 25% and 55% lower, respectively, than in healthy subjects. Also, the mean tigecycline AUC was 50% higher in the Child Pugh B subjects and 105% higher in the Child Pugh C subjects. No dosage adjustment is warranted in patients with mild-to-moderate hepatic impairment (Child Pugh A and Child Pugh B). However, in patients with severe hepatic impairment (Child Pugh C), the dose of tigecycline should be reduced. (See **Dosage and Administration.**)
Open-label, nonrandomized, evaluation of the potential drug interaction between tigecycline 100 mg + 50 mg q12h and digoxin 0.5 mg + 0.25 mg q24h (3074A1-111-US, CSR-53262)	1-hour infusions of tigecycline 100 mg (n=20) 100 mg + 50 mg q12h administered with digoxin (n=20) oral digoxin 0.5 mg + 0.25 mg q24h (n=20) 0.25 mg	30/30 (30M/19B, 1O, 10W)	Digoxin did not affect the tigecycline clearance or AUC. Tigecycline slightly reduced digoxin C_{max} by 13%, but it did not affect the digoxin clearance, AUC, or concentrations at therapeutic drug monitoring times (12 to 24 hours postdose). Tigecycline did not alter digoxin's effects on ECG intervals. Therefore, based on the results of this study, tigecycline and digoxin can be

Study	Dose (n Analyzed)	Enrolled/Analyzed (Sex/Race)	Results and Conclusions
	administered with tigecycline (n=20)		safely coadministered, and no dosage adjustment of either drug is warranted.
Open-label, nonrandomized, evaluation of the potential drug interaction between tigecycline 100 mg + 50 mg q12h and warfarin 25 mg single-dose (3074A1-115-US, CSR-52363)	1-hour infusions of tigecycline 100 mg + 50 mg q12h (n=13) 50 mg q12h plus warfarin (n=11) oral warfarin 25 mg (n=19) 25 mg plus tigecycline (n=8)	19/19 (19M/3A, 5B, 1O, 10W)	Warfarin did not affect the pharmacokinetic profile of tigecycline. Tigecycline increased the AUC of R-warfarin and S-warfarin by 68% and 29%, respectively, but warfarin's effects on INR were not altered by tigecycline. Therefore, based on the results of this study, no dosage adjustment is warranted with coadministration of tigecycline and warfarin. However, the proper level of anticoagulant activity should be monitored whenever patient treatment is altered, such as initiating treatment with another drug.
Safety analyses of tigecycline-treated subjects in 3 double-blind, randomized studies. (3074A1-308-WW, 3074A1-311-WW, and 3074A1-313-WW, CSR-69432).	Tigecycline infusion: an initial 100-mg loading dose followed by 50 mg q12h Safety analyses: n=412	Safety: --/412 (160F, 252M/ 30B, 67H, 14O, 301W)	Gender and increased tigecycline exposure was significantly associated with the occurrence of nausea and/or vomiting. Women were more likely to experience nausea and/or vomiting than men. After adjusting for subject sex, subjects with AUC_{0-24} values greater than or equal to 6.48 mg•hr/L were estimated to have 7.5 times the odds of experiencing nausea and/or vomiting compared to those with AUC_{0-24} values below 3.21 mg•hr/L. Despite achieving statistical significance, the relationship between AUC_{0-24} and maximum change in total bilirubin is unlikely to be of clinical significance at clinically achievable tigecycline exposures.

A=Asian, B=Black, ESRD=End-Stage Renal Disease, F=Female, H=Hispanic, M=Male, O=Other, W=White

MICROBIOLOGY

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.

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 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 in testing medium that is fresh (<12h old). The MIC values should be interpreted according to the criteria provided in Table 16.

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 16.

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

Table 16: 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)	≤0.5[a]	-	-	≥19	-	-
Streptococcus spp. other than *S. pneumoniae*	≤0.25[a]	-	-	≥19	-	-
Streptococcus pneumoniae (penicillin-susceptible isolates only)	≤0.06[a]			≥19	-	-
Enterococcus faecalis (vancomycin-susceptible)	≤0.25[a]	-	-	≥19	-	-
Enterobacteriaceae[b]	≤2	4	≥8	≥19	15-18	≤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 "non-susceptible" category should be submitted to a reference laboratory for further testing.
[b.]. Tigecycline has decreased *in vitro* activity against *Proteus* spp., *Providencia* spp. & *Morganella* spp.
[c.] Agar Dilution

A report of "Susceptible" (S) indicates that the pathogen is likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable. 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 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 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 17. For the diffusion technique using the 15 µg tigecycline disk, laboratories should use the criteria provided in Table 17 to test quality control strains.

Table 17: Acceptable Quality Control Ranges for Susceptibility Testing

QC organism	Minimum Inhibitory Concentrations (µg/mL)	Disk Diffusion (zone diameters in mm)
Staphylococcus aureus ATCC 25923 [a]	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
Streptococcus pneumoniae ATCC 49619 [b]	0.016-0.12	23-29
Haemophilus influenzae ATCC 49247[c]	0.06-0.5	23-31
Neisseria gonorrhoeae ATCC 49226 [d]	Not Applicable	30-40
Bacteroides fragilis ATCC 25285 [e]	0.12-1	Not Applicable
Bacteroides thetaiotaomicron ATCC 29741 [e]	0.5-2	Not Applicable
Eubacterium lentum ATCC 43055 [e]	0.06-0.5	Not Applicable
Clostridium difficile[ae] ATCC 70057	0.12-1	Not Applicable

[a.] ATCC = American Type Culture Collection
[b.] Testing of *S. pneumoniae* by broth dilution method should be performed with fresh Mueller-Hinton broth supplemented with 5% lysed horse blood or agar dilution method supplemented with 5% sheep blood and a McFarland 0.5 standard inoculum
[c.] Testing of *H. influenzae* should be performed in fresh Haemophilus Test Medium, broth or agar.
[d.]. Testing of *N. gonorrhoeae* should be performed in GC agar base medium supplemented with 1% defined growth supplement.

[e.]. Testing of anaerobes should be performed by agar dilution only.

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 in Table 18 and Table 19 provide only approximate guidance on the probability as to whether the micro-organism will be susceptible to tigecycline or not.

A summary of *in vitro* activities of tigecycline against recent Gram-positive and Gram-negative aerobic clinical isolates performed with reference methods is presented in Table 18 and Table 19 respectively.

Table 18 indicates tigecycline is active against strains of microorganisms both *in vitro* and in clinical infections. Table 19 indicates *in vitro* MICs of tigecycline against microorganisms, however the effectiveness of tigecycline in treating clinical indications due to these microorganisms have not been established in adequate and well-controlled studies. Tigecycline has demonstrated decreased *in vitro* activity against *Proteus* spp., *Providencia* spp. & *Morganella* spp. *Pseudomonas aeruginosa* is inherently resistant to tigecycline.

Table 18: *In vitro* activities of tigecycline against organisms for which tigecycline has demonstrated clinical efficacy

Organism	Number of Isolates	Range	MIC (µg/mL) 50%	90%
Enterococcus faecalis (VSE)	159	0.03-0.25	0.06	0.12
Staphylococcus aureus (MSSA)	160	0.03-0.25	0.12	0.12
Staphylococcus aureus (MRSA)	165	0.03-2	0.12	0.25
Streptococcus agalactiae	115	≤0.03-0.06	≤0.03	0.06
Streptococcus pneumoniae (penicillin-susceptible isolates)	189	0.004-0.25	0.015	0.06
Streptococcus pyogenes	176	≤0.03-0.06	≤0.03	0.06
Citrobacter freundii	160	0.03-8	0.25	0.5
Enterobacter cloacae	160	0.25-8	0.5	0.5
Escherichia coli	208	0.06-1	0.12	0.5
Haemophilus influenzae	204	0.06-1	0.25	0.5
Klebsiella pneumoniae	180	0.25-4	0.5	1
Clostridium perfringens [a]	89	≤0.06-16	0.5	2
Peptostreptococcus micros [a]	53	≤0.06-0.25	≤0.06	≤0.06
Bacteroides fragilis [a]	943	≤0.06-32	1	8
Bacteroides thetaiotaomicron [a]	451	≤0.06-32	1	8
Bacteroides uniformis [a]	134	≤0.06-16	0.5	4
Bacteroides vulgatus [a]	159	≤0.06-8	1	4
Chlamydia pneumoniae	10	0.12-0.25	0.12	0.12
Mycoplasma pneumoniae[b]	30	0.06-0.25	0.12	0.25

[a.] MICs of anaerobic bacteria were determined by agar dilution
[b.] MICs of *M. pneumoniae* were determined by agar dilution

Table 19: *In vitro* activities of tigecycline against recent clinical isolates performed with reference methods, however clinical efficacy has not yet been demonstrated

Organism	Number of Isolates	Range	MIC (µg/mL) 50%	90%
Gram-positive aerobes				
Enterococcus avium	140	≤0.016-0.25	0.06	0.12
Enterococcus casseliflavus	100	0.03-0.25	0.06	0.12
Enterococcus faecalis (VRE)	147	≤0.016-0.5	0.06	0.12
Enterococcus faecium (VSE)	171	≤0.03-0.5	0.06	0.12
Enterococcus faecium (VRE)	155	≤0.03-0.25	≤0.03	0.12
Enterococcus gallinarium	164	≤0.03-0.25	0.06	0.12
Staphylococcus epidermidis (MSSE)	159	0.03-2	0.12	0.5
Staphylococcus epidermidis (MRSE)	155	0.03-1	0.12	0.5
Staphylococcus haemolyticus	166	≤0.016-2	0.25	0.5
Streptococcus pneumoniae (penicillin-resistant isolates)	269	≤0.03-0.25	≤0.03	0.06
Listeria monocytogenes	220	≤0.03-0.12	0.06	0.12
Gram-negative aerobes				
Citrobacter koseri (*C. diversus*)	175	0.06-2	0.25	0.5
Enterobacter aerogenes	161	0.03-4	0.25	1
Haemophilus parainfluenzae	166	0.06-2	0.5	1
Klebsiella oxytoca	140	0.12-2	0.25	0.5
Legionella pneumophila[a]	50	2-8	4	8
Moraxella catarrhalis	240	≤0.03-0.25	0.06	0.12
Morganella morganii[b]	145	0.12-8	1	4
Neisseria meningitidis	298	≤0.03-0.5	≤0.03	0.12
Proteus mirabilis[b]	160	0.5-16	4	8
Proteus vulgaris[b]	220	0.5-8	2	4
Providencia stuartii[b]	232	0.12-64	2	4
Providencia rettgeri[b]	192	0.12-16	2	4
Salmonella enterica ser. Enteritidis	299	0.12-2	0.5	1
Salmonella enterica ser. Paratyphi	261	0.12-2	0.5	0.5
Salmonella enterica ser. Typhimurium	269	0.12-2	0.5	1
Salmonella enterica ser. Typhi	304	0.06-1	0.25	0.5
Serratia marcescens	160	0.25-8	1	2
Acinetobacter baumannii	158	0.03-4	0.5	2

Organism	Number of Isolates	Range	MIC (µg/mL) 50%	90%
Aeromonas hydrophila	142	0.06-1	0.25	0.5
Pasteurella multocida	126	≤0.03-0.25	≤0.03	0.12
Pseudomonas aeruginosa [c]	160	0.25-32	8	16
Stenotrophomonas maltophilia	160	0.06-16	0.5	2
Gram-positive anaerobes				
Peptostreptococcus spp. [d]	84	≤0.06-2	≤0.06	0.25
Eubacterium lentum [d]	48	<0.06-1	0.25	0.5
Propionibacterium spp. [d]	44	<0.06-0.5	≤0.06	0.5
Gram-negative anaerobes				
B. fragilis group [d]	46	≤0.06-16	0.5	2
Bacteroides caccae [d]	98	0.5-64	1	8
Bacteroides distasonis [d]	161	0.12-16	2	8
Bacteroides ovatus [d]	162	0.03-32	1	8
Prevotella spp. [d]	108	0.015-5	0.25	0.5
nontuberculous *Mycobacteria* spp.				
M. abscessus	38	≤ 0.06-1	≤ 0.12	0.25
M. chelonae	48	≤ 0.06 - ≤ 0.25	≤ 0.06	< 0.12
M. fortuitum	36	≤ 0.06 - ≤ 0.25	≤ 0.06	< 0.12

[a] Tigecycline is inactivated by the testing medium required to grow *Legionella*
[b] Tigecycline has decreased *in vitro* activity against *Proteus* spp., *Morganella* spp. and *Providencia* spp.
[c]. No significant *in vitro* activity against *P. aeruginosa* has been demonstrated.
[d.] MICs of anaerobic bacteria were determined by agar dilution

TOXICOLOGY

The toxicity of tigecycline administered IV was evaluated in single-dose studies in mice and rats, tolerability/pilot studies in rats, rabbits, dogs, and monkeys, and repeat-dose (2-week, 2-week with 3-week recovery, and 13-week) studies in rats and dogs; the 2-week and 13-week studies also evaluated toxicokinetics. Special toxicity studies with tigecycline were conducted that assessed the following: hematotoxicity recoverability in dogs; phototoxicity in rats; emetogenic potential in the shrew; antigenicity in guinea pigs, mice and rats; *in vitro* blood compatibility in rat, dog, and human blood; and cellular and mitochondrial protein synthesis in rat and dog hepatocytes. Genotoxic potential was evaluated in mammalian *in vitro* and *in vivo* assays, but not in bacterial reverse mutation assays due to the antibacterial action of tigecycline. Cross-sensitization with structurally-related tetracyclines has not been evaluated. Functional immunotoxicity has not been evaluated.

The toxicities of the human metabolites (tigecycline glucuronide and N-acetyl 9-aminominocycline) have not been evaluated following the administration of tigecycline (see Animal Pharmacology Section).

Bolus intravenous administration of tigecycline has been associated with clinical observations consistent with histamine release in both the rat and dog species (edema, erythema, itching, labored breathing, red pigmentation around the eyes, nose, and mouth, salivation, swollen areas {muzzle, paws, pinnae, peri-orbital region}). These effects were observed predominantly at dosages $\underline{\geq}$ 20 mg/kg/day in rats and $\underline{\geq}$ 5 mg/kg/day in dogs, corresponding to animal:human exposure ratio (ER) 14.3 and 2.8 , based on AUC. Serum histamine levels were elevated at between 5 to 20 minutes post-dose in the dog, but not the rat. Other possible histamine-related changes, included lacrimation, vocalization, emesis, and fecal changes.

The observed decreases in total protein, albumin, and globulin might be attributed in part to an inhibition of mitochondrial protein synthesis in mammalian cells. The results of an exploratory *in vitro* study suggest that high concentrations of tigecycline ($\underline{\geq}$ 10 µg/mL) may inhibit mitochondrial protein synthesis *in vivo*.

Yellow discoloration of bone was observed in the 2- and 13-week studies in rats at ≥ 42.3 and 6 mg/kg/day, respectively.

In rats, injection site lesions were observed at tigecycline concentrations ≥ 25 mg/mL in the 2-week studies (dosages of 30 and 70 mg/kg/day) and at tigecycline concentrations ≥ 3 mg/mL in the 13-week study (dosages of 6 and 20 mg/kg/day). These effects were considered to result from the repeated injection of tigecycline into a small vessel.

Toxicologically significant erythrocyte, reticulocyte, platelet, and/or leukocyte decreases without histopathologic bone marrow correlates were seen in the 13-week rat study at ≥ 6 mg/kg/day, corresponding to ERs of 3.3 (male) and 2.4 (female) based on AUC, and in a 2-week dog study at ≥ 5 mg/kg/day (ER of 2.8, based on AUC). Histopathologic correlates in the bone marrow to the hematologic changes were observed at ≥ 30 mg/kg/day in the 2-week rat study and at ≥ 12 mg/kg/day in the 2-week dog study, corresponding to ERs ≥ 8.2 and ≥ 9.8, respectively. Decreased leukocytes was seen in rats at 5 mg/kg/day (ER of 1.2, based on AUC), but was not considered toxicologically significant due to the small magnitude of change. These hematologic alterations were shown to be reversible within a 3-week recovery period after 2 weeks of dosing.

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

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

Mutagenicity: No mutagenic or clastogenic potential was found. Tigecycline was not genotoxic in 4 *in vitro* assays (chromosome aberration assay in CHO cells, forward mutation assay in CHO cells, and 2 forward mutation assays in mouse lymphoma cells) and 1 *in vivo* assay (mouse micronucleus). The genotoxic potential of elevated levels of tigecycline drug product impurities was not evaluated.

Impairment of Fertility: Tigecycline did not affect mating, fertility, ovaries, or estrous cycles in rats at up to 12 mg/kg/day (ER of 4.7 based on AUC).

Developmental Toxicity

Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies in the rat, ^{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 in mice at 5 mg/kg/day, in rats at 12 mg/kg/day (ER of 4.7, based on AUC) and in rabbits at 4 mg/kg/day (ER of 1.1, based on AUC). An increased incidence of minor skeletal anomalies (delays in bone ossification) occurred in rats at 4 mg/kg/day (ER of 1.8, based on AUC) and in rabbits, together with an increased incidence of fetal loss, at 4 mg/kg/day (ER of 1.1, based on AUC), a dosage producing minimal maternal toxicity.

The overall animal:human exposure ratios, based on AUC_{0-24}, in the 13-week general toxicity studies at the NTEL for rats (2 mg/kg/day) was 1.0 and at the NOAEL (1.5 mg/kg/day) for dogs was 0.7. Human exposure data were projected based on a steady state AUC_{0-12} (50 mg q12h) of 3.07 µg•h/mL, which is equivalent to an AUC_{0-24} of 6.1 µg•h/mL (total daily dose of 100 mg).

Table 20: Toxicology Study Overview

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
Single-Dose GTR-31860	Mice; CD-1; 3/sex/dosage; 43 – 46 days; 30 - 34 g (males), 22 – 25 g (females)	IV, bolus (needle); 1 day	87.5 mg/kg (35 mg/mL), 175 mg/kg (35 mg/mL); 2.5 – 5 mL/kg; pH of the dosing solution was 8.1	• Evaluations were based on mortality, clinical observations, body weight, and macroscopic examination. • Animals were observed for up to 15 days after dosing. • All animals died at 175 mg/kg. • One female died at 87.5 mg/kg. • Decreased motor activity, ptosis, dyspnea, exophthalmia, lacrimation, and red pigmentation around eye(s) at 87.5 mg/kg. • ~ LD50 (mg/kg): 124 (male), 98 (female).
Single-Dose GTR-31861	Rats; S-D; 3/sex/dosage; 43 – 46 days; 186 – 241 g (males), 159 – 182 g (females)	IV, bolus (needle); 1 day	75 mg/kg (15 mg/mL), 150 mg/kg (60 mg/mL), 300 mg/kg (60 mg/mL); 2.5 – 5 mL/kg; pH of the dosing solutions ranged from 8.0 to 8.1	• Evaluations were based on mortality, clinical observations, body weight, and macroscopic examination. • Animals were observed for up to 15 days after dosing. • All animals died at ≥ 150 mg/kg. No mortality at 75 mg/kg. • Immobility, decreased motor activity, ptosis, dyspnea, exophthalmia, erythema (ears, tail, and feet), low carriage, and edema (feet and head). • ~LD50 (mg/kg): 106 (male and female).
Repeat-Dose MIRACL-26228	Rats; S-D; 6M/dosage; for TK, 6 and 4 M at 42.3 and 84.7 mg/kg/day; ~ 9 weeks; 269 – 334 g	IV, two 1-h infusions, 8 h apart (catheter); twice daily for 14 days	42.3[e] (2.25 mg/mL), 84.7[e] (4.5 mg/mL), 169[e] (9 mg/mL); 0.17 mL/kg/min for 60 minutes	• Evaluations were based on mortality, clinical observations, body weight, food consumption, TK, and macroscopic postmortem examinations. • Mean day 15 values for dosages 42.3 and 84.7 mg/kg/day were, respectively: C_{max} (µg/mL): 19, 39 AUC_{0-24}(µg•h/mL): 35, 105.

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
Repeat-Dose GTR-31608	Rats; S-D; 15/sex/dosage; for TK: 9M/dosage, 9F at 30 mg/kg/day; ~ 7 weeks; 219 - 275 g (males), 153 – 199 g (females)	IV, bolus (needle); once daily for 14 or 15 days	0 (0 mg/mL), 5 (5 mg/mL),[f] 30 (30 mg/mL), 70 (70 mg/mL); 1 mL/kg; pH of the dosing solutions ranged from 7.9 to 8.1	• Evaluations were based on mortality, clinical observations, body weight, food consumption, ophthalmoscopy, hematology, clinical chemistry, TK, organ weights, and macroscopic and microscopic postmortem examinations. • No tigecycline-related mortality. • Injection site lesions at 70 mg/kg/day required the euthanasia of 3 animals. • Clinical signs (salivation, red pigmentation around the eyes, nose, and mouth, lacrimation, soft feces, and erythema) were observed at ≥ 30 mg/kg/day. • Bright yellow urine accompanied by yellow discoloration of the perineal pelage was seen at ≥ 30 mg/kg/day, hematuria, and blood in the feces were seen at ≥ 5 mg/kg/day. • At 30 and 70 mg/kg/day, injection site lesions, including hemorrhage, inflammation, venous thrombosis, and venous necrosis occurred with increased incidence and frequency. • Red pigmentation around the genitalia occurred in a few rats at 70 mg/kg/day. • Decreased body weight gain occurred in males at ≥ 30 mg/kg/day (ie, treated animals did not lose weight, but had lower body weights compared with controls at the end of the dosing period). Food consumption was reduced at 70 mg/kg/day in males. • Toxicologically significant decreases in RBC parameters, reticulocytes, platelets, and WBCs as well as decreased serum proteins (both albumin and globulin) occurred at ≥ 30 mg/kg/day. A slight increase (34%) in fibrinogen occurred in males at 70 mg/kg/day. • Yellow discoloration of the bone and decreased thymus size

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
				were seen at 70 mg/kg/day.
Repeat-Dose GTR-31608 (con't)				• Changes in bone marrow (erythroid hypoplasia), spleen (erythroid hypoplasia), and kidney (increased incidence of tubular basophilia) as well as lymphoid and thymus atrophy occurred at ≥ 30 mg/kg/day. • The NTEL was 5 mg/kg/day. • Tigecycline AUC_{0-24} may be underestimated by approximately 20% due to documented sample degradation. • Mean day 14 values for dosages 5, 30, and 70 mg/kg/day, respectively were: C_{5min} (µg/mL): males: 7.46, 119, 152 females: na, 86.9, na AUC_{0-24}(µg•h/mL): males: 7.12, 65.9, 129 females: na, 50, na.
Repeat-Dose RPT-42195	Rats; S-D; 15/sex/dosage, 5/sex/dosage retained for recovery; ~ 6 weeks; 263 – 301 g (males), 162 – 207 g (females)	IV, bolus (needle); once daily for 14 days, with 3-week recovery	0 (0 mg/mL), 20 (10 mg/mL), 50 (25 mg/mL), 70 (35 mg/mL); 2 mL/kg; pH of the dosing solutions ranged from 7.81 to 7.90	• Evaluations were based on mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry, organ weights, and macroscopic and microscopic postmortem examinations. • Mortality at 70 mg/kg/day was due to compound-related toxicity affecting various organ systems, primarily the hemopoietic system. • Clinical observations were slight to severe salivation, decreased activity, labored breathing, pale skin, black fur staining around the muzzle, skin scabs, and yellow fur staining at ≥ 20 mg/kg/day and swollen tail, partly closed eyes, red liquid ocular discharge, abnormal gait, red fur staining, circling, tail skin lesion, uncoordinated, non-

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
Repeat-Dose RPT-42195 (cont'd)				sustained convulsions, swollen muzzle, lying on side, slight dehydration, hunched posture, shallow breathing, cold to touch, pale eyes, teeth grinding, weakness, loss of consciousness, and moderate to severe tremors at ≥ 50 mg/kg/day. • Weight loss occurred at > 50 mg/kg/day while decreased body weight gain was seen at > 20 mg/kg/day. • Decreased food consumption occurred at 70 mg/kg/day. • Decreases in RBC parameters and lack of reticulocyte response occurred at > 20 mg/kg/day. Toxicologically significant decreases in RBC parameters and reticulocytes occurred at 70 mg/kg/day. Decreased platelets, and WBCs, as well as decreased serum proteins (albumin and globulin) occurred at ≥ 20 mg/kg/day. • Decreased triglycerides occurred in males at > 20 mg/kg/day. • Increased bilirubin occurred at > 50 mg/kg/day. Decreased unsaturated iron binding capacity occurred in males at 70 mg/kg/day. • At scheduled necropsy, macroscopic yellow discoloration of bone, small thymus, and dark and/or depressed areas in the mucosa of the stomach occurred in rats given ≥ 50 mg/kg/day. The lesions in the thymus and stomach correlated microscopically with lymphoid atrophy and mucosal erosion, respectively. • Tigecycline-related microscopic findings in other tissues at scheduled necropsy included minimal to marked bone marrow hypocellularity and decreased extramedullary

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
Repeat-Dose RPT-42195 (cont'd)				hematopoiesis in the spleen at ≥ 50 mg/kg/day, minimal atrial thrombosis in the heart of 1 rat at 70 mg/kg/day; minimal to moderate cortical tubular degeneration, tubular single-cell necrosis, and/or granular casts in the kidney at ≥ 20 mg/kg/day; and lymphoid atrophy of the mesenteric lymph node and spleen at 70 mg/kg/day and thymus at ≥ 20 mg/kg/day. There was an increased incidence of minimal to moderate inflammation in the heart (myocardial) and prostate gland at 70 mg/kg/day and at ≥ 50 mg/kg/day, respectively. The heart lesions (myocardial inflammation) were not attributed to a direct toxic effect of the compound on the heart. The heart lesions were considered secondary to tigecycline-induced histamine release and its effects on the cardiovascular system leading to myocardial ischemia and subsequent degeneration and necrosis (and mineralization in 1 male that was found dead). Also, minimal to massive thrombosis, mural necrosis, and perivascular hemorrhage, fibrin exudation, and inflammation occurred at the injection site with increased incidence and/or severity in treated rats compared with controls. • Endocortical proliferation, fibrosis, and/or cortical hyperostosis were observed in the femoral-tibial joint of the 1 surviving male rat at 70 mg/kg/day and 3 of 10 male rats at 50 mg/kg/day. • Evidence of reversibility by the end of the 3-week recovery period was observed for most tigecycline-related antemortem and postmortem changes, except that red cell distribution width remained elevated, heart lesions (myocardial inflammation, atrial thrombosis in a single

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
				animal) were still evident at > 50 mg/kg/day at a greater incidence than in control, and yellow discoloration of bones was still evident (50 mg/kg/day).
Repeat-Dose RPT-41074	Rats; S-D; 15/sex/dosage; for TK, 21 males at 2 and 20 mg/kg/day, 21/sex at 6 mg/kg/day; ~ 6 weeks; 177 – 214 g (males), 138 – 168 g (females)	IV, bolus (needle); once daily for 13 weeks	0 (0 mg/mL), 2 (1 mg/mL), 6 (3 mg/mL), 20 (10 mg/mL); 2 mL/kg; pH of the dosing solutions ranged from 7.71 to 7.96	• Evaluations were based on mortality, clinical observations, body weight, food consumption, ophthalmoscopy, hematology, clinical chemistry, TK, organ weights, and macroscopic and microscopic postmortem examinations. • Clinical signs (vocalization) were observed at 20 mg/kg/day. • Decreased body-weight gain and body weights were observed at 20 mg/kg/day (body-weight loss did not occur). • Toxicologically significant decreases in RBC parameters, reticulocytes, platelets, and WBCs as well as decreased serum proteins (both albumin and globulin) occurred at ≥ 6 mg/kg/day. Yellow discoloration of the bone was seen at ≥ 6 mg/kg/day. Decreased thymus and spleen weights occurred at 20 mg/kg/day. Injection site lesions (scabs, ulceration, necrosis) occurred at ≥ 6 mg/kg/day. • Minimal lymphoid atrophy occurred in the thymus at 20 mg/kg/day. Although microscopic changes in the bone marrow and spleen were not observed in this study, the similar pattern of hematologic changes strongly suggests the same target organ involvement. • The NTEL was 2 mg/kg/day. • Mean day 90 values for dosages 2, 6, and 20 mg/kg/day were, respectively: C_{5min} (µg/mL): males: 2.41, 12.7, 86.5 females: na, 11.2 , na AUC_{0-24} (µg•h/mL):

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
				males: 6.23, 19.9, 87.3 females: na, 14.6, na.
Repeat-Dose Pilot GTR-30663	Dogs; Beagle; 2/sex/dosage; ~5 – 6 months; 6.5 – 9.0 kg	IV, bolus (needle); once daily for 14 days	0 (0 mg/mL), 2 (5 mg/mL), 5 (5 mg/mL), 12 (5 mg/mL); 0.4, 1.0, or 2.4 mL/kg	• Evaluations were based on mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry, urinalysis, TK, organ weights, and macroscopic and microscopic postmortem examinations. • Mean day 15 values for dosages 2, 5, and 12 mg/kg/day were, respectively: C_{5min} (µg/mL): 2.76, 11.12, 42.46 AUC $_{0-\infty}$ (µg•h/mL): 6.08, 12.3, 34.
Repeat-Dose Pivotal GTR-31609	Dogs; Beagle; 3/sex/dosage; ~7.5 months; 10.0 – 11.0 kg (males), 7.8 – 10.7 kg (females)	IV, bolus (needle); once daily for 14 or 15 days	0 (0 mg/mL), 2 (1 mg/mL), 5 (2.5 mg/mL), 12 (6 mg/mL), 20 (10 mg/mL); 2 mL/kg; pH of dosing solutions ranged from 7.9 to 8.0	• Evaluations were based on mortality, clinical observations, body weight, food consumption, ophthalmoscopy, electrocardiogram, hematology, clinical chemistry, urinalysis, TK, organ weights, and macroscopic and microscopic postmortem examinations. • Four (4) of 6 dogs at 20 mg/kg/day were euthanized during week 2 due to severe physical debilitation. • Fecal alterations occurred at ≥ 2 mg/kg/day. Clinical signs (erythema, salivation, swollen area, and emesis) occurred at ≥ 5 mg/kg/day. Clinical signs (hematuria, blood in feces, decreased feces, decreased motor activity) occurred at > 12 mg/kg/day. Clinical signs evident only at 20 mg/kg/day included excessive vocalization, favors limb, lack of fecal output, liquid feces, hematemesis, cool to touch, hunched and/or thin appearance. • Body-weight loss and decreased food consumption were observed at ≥ 12 mg/kg/day. • Decreased platelets, reticulocytes, and WBCs occurred at > 5 mg/kg/day; these effects were toxicologically significant at

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
Repeat-Dose Pivotal GTR-31609 (cont'd)				≥ 12 mg/kg/day. • Thrombocytopenia occurred at 20 mg/kg/day. • Increased APTT, increased cholesterol, and decreased glucose occurred at > 12 mg/kg/day. • Increased fibrinogen and inorganic phosphorous, decreased serum proteins (albumin and globulin) and thyroxine occurred at 20 mg/kg/day. • Decreased weights of heart, kidney, testes, and increased adrenal weight occurred at 20 mg/kg/day. • Lymphoid depletion/atrophy (lymph nodes, spleen, thymus) occurred at ≥ 12 mg/kg/day. • Microscopic findings consisted of changes in the GI tract (villus atrophy and cryptic degeneration and regeneration) and bone marrow (erythroid, megakaryocytic, and myeloid hypoplasia), lymphoid atrophy, crypt dilation, edema of the lamina propria, and/or acute inflammation of the small intestine occurred at ≥ 12 mg/kg/day. • Additional effects observed at ≥ 12 mg/kg/day (vacuolation of hepatocytes, pancreatic edema, erosion and ulceration or inflammation of the mouth and esophagus) were considered secondary to decreased food consumption, vomiting, weight loss, lower serum proteins, and stress. • The NTEL was 5 mg/kg/day. • Mean day 14 values for dosages 2, 5, 12 and 20 mg/kg/day, respectively were: C_{5min} (µg/mL): 3.17, 14.9, 56.2, 91.4 AUC_{0-24}(µg•h/mL): 5.48, 17.1, 59.9, 149.
Repeat-Dose Pivotal	Dogs; Beagle; 6/sex/dosage,	IV, bolus (needle); once daily for	0 (0 mg/mL), 5 (5 mg/mL),	• Evaluations were based on mortality, clinical observations, body weight, food consumption, hematology, clinical

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
RPT-42488	3/sex/dosage retained for recovery; ~ 6 – 7 months; 9.0 – 12.1 kg (males), 5.8 – 9.8 kg (females)	14 days, 3-week recovery	12 (12 mg/mL); 1 mL/kg; pH of dosing solutions ranged from 7.79 to 7.88	chemistry, urinalysis, histamine analysis, organ weights, and macroscopic and microscopic postmortem examinations. • During the dosing period, clinical observations included reddening, raised bumps, and/or swelling of the paws, pinnae, muzzle, abdomen, cranium, dorsal thoracic, ventral cervical, and/or periorbital region; itching; emesis; fecal alterations (soft, liquid, and mucoid); salivation; decreased activity, and slight tremors at ≥ 5 mg/kg/day. Labored/shallow breathing, cool to touch, and tremors occurred at 12 mg/kg/day. • Body-weight loss occurred at 12 mg/kg/day • Decreased food consumption was observed at ≥ 5 mg/kg/day. • Toxicologically significant decreases in RBC parameters, WBCs, and platelets, occurred at ≥ 5 mg/kg/day. Decreased reticulocytes, total proteins (albumin and globulin), and increased MPV occurred ≥ 5 mg/kg/day. • Increased BUN, creatinine, and prolonged APTT (in males) occurred at 12 mg/kg/day. • Increased incidence and/or severity of hematuria occurred at > 5 mg/kg/day at the end of the dosing period. • Serum histamine levels were increased at ≥ 5 mg/kg/day on days 1 through 7 at both 5 minutes and 20 minutes after dosing. • Microscopic findings consisted of lymphoid atrophy in the thymus and renal tubular degeneration at ≥ 5 and 12 mg/kg/day, respectively. • Recovery of the antemortem findings was evident by the

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
Repeat-Dose Pivotal RPT-42488 (cont'd)				end of the 3-week compound-free period. • Evidence of reversibility was observed for tigecycline-related postmortem changes, except for a higher incidence/severity of hematuria at the end of the recovery period at > 5 mg/kg/day; the toxicologic significance of this finding is uncertain. Also, the decreased incidence and/or severity of thymic lymphoid atrophy (compared with that observed at the end of dosing) and the finding of tubular basophilia (indicator of renal tubular regeneration) accompanied by decreased BUN and creatinine levels (compared with the end of dosing) were indicative of partial recovery in these organs.
Repeat-Dose Pivotal RPT-41664	Dogs; Beagle; 3/sex/dosage; ~ 6 – 7 months; 7.2 – 8.7 kg (males), 6.2 – 7.5 kg (females)	IV, bolus (needle); once daily for 13 weeks	0 (0 mg/mL), 0.5 (0.5 mg/mL), 1.5 (1.5 mg/mL), 5 (5 mg/mL); 1 mL/kg; pH of dosing solutions ranged from 7.60 to 7.89	• Evaluations were based on mortality, clinical observations, body weight, food consumption, ophthalmoscopy, electrocardiogram, hematology, clinical chemistry, urinalysis, TK, organ weights, and macroscopic and microscopic postmortetm examinations. • Tigecycline-related clinical observations consisted of areas of reddening and/or swelling and/or raised bumps of the paws, pinnae, muzzle, soft tissues around the cranium, and/or periorbital area, and itching/scratching in all males and females at 5 mg/kg/day. • Increased red cell distribution width, decreased WBC, decreased neutrophils and increased prothrombin time occurred at 5 mg/kg/day, however the magnitude of these changes was not considered toxicologically relevant. • Lymphoid atrophy of the thymus occurred at 5 mg/kg/day. • The NOAEL/NTEL was 1.5 mg/kg/day.

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
Repeat-Dose Pivotal RPT-41664 (cont'd)				• Mean day 75 values for dosages 0.5, 1.5, and 5 mg/kg/day were, respectively: C_{5min} (µg/mL): 0.55, 1.85, 15.7 AUC_{0-24} (µg•h/mL): 1.61, 4.48, 19.3.
Genotoxicity				
Forward Mutation Assay	CHO Cells	*In Vitro*	25 to 2000 µg/mL; NA	• Negative
Forward Mutation Assay	Mouse Lymphoma Cells	*In Vitro*	6.25 to 500 µg/mL; NA	• Negative
Forward Mutation Assay	Mouse Lymphoma Cells	*In Vitro*	6.25 to 400 µg/mL; NA	• Negative
Chromosome Aberration	CHO Cells	*In Vitro*	0.291 to 1000 µg/mL; NA	• Negative
Micronucleus Assay	Mice; CD-1 Bone Marrow Cells	IV	37.5, 75, 150; single dose	• Negative
Reproductive Toxicity				
Dose-Ranging Fertility and Developmental Toxicity GTR-32617	Rats; S-D; 10/sex/dosage; 10 – 12 weeks; 358 – 414 g (males), 198 - 268 g (females)	IV, bolus (needle); M: once daily for 4 weeks prior to cohabitation and continuing throughout cohabitation, F: once daily 2 weeks prior to cohabitation,	0 (0 mg/mL), 5 (5 mg/mL), 15 (15 mg/mL), 45/30 (45/30mg/mL); 1 mL/kg; pH of the dosing solutions ranged from 7.8 to 8.0	• Evaluations were based on mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry, estrous cycles, mating performance, gravid uterine weight, hysterotomy findings on GD 21, prostate weights, and macroscopic and selected microscopic postmortem examinations. Fetal evaluations were based on gender, weight, and gross external and palatal anomalies. • In females, body-weight gains were reduced at ≥ 5 mg/kg/day during gestation. At 15 and 30 mg/kg/day, this period of reduced body-weight gain in females was

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
Dose-Ranging Fertility and Developmental Toxicity GTR-32617 (cont'd)		continuing throughout cohabitation, and through GD 16		interrelated with reduced fetal weights and/or increased incidence of resorptions that occurred in these groups. • Microscopically, the incidence and severity (slight to mild) of testicular tubular degeneration were marginally increased in males at 45/30 mg/kg/day; hypospermia of the epididymides was observed in 2 of these rats at 45/30 mg/kg/day. Injection site cellulitis was observed at ≥ 15 mg/kg/day. • There was a slight reduction in the number of viable fetuses per dam at ≥ 15 resulting from an increase in the number of early resorptions and preimplantation loss.
Fertility and Developmental Toxicity RPT-42298	Rats; S-D; 25/sex/dosage, 21F/dosage for TK; 47 – 51 days (males). 68 – 72 days (females); 233 – 289 g (males), 189 – 260 g (females)	IV, bolus (needle); M: once daily for 10 weeks prior to cohabitation, and until 1 day prior to necropsy, F: once daily for 2 weeks prior to cohabitation and through GD 17	0 (0 mg/mL), 1 (1 mg/mL), 4 (4 mg/mL), 12 (12 mg/mL); 1 mL/kg; pH of the dosing solutions ranged from 7.74 to 7.94	• Evaluations were based on mortality, clinical observations, body weight, food consumption, estrous cycles, fecundity parameters, gravid uterine weight, hysterotomy findings, selected organ weights, examination of spermatozoa, TK, and macroscopic and selected microscopic (males) postmortem examinations. Fetal evaluations were based on gender, weight, and gross external, visceral, and skeletal examinations. • No effects on mating or fertility, and not teratogenic. • Tigecycline-related clinical signs (including fur discoloration of the muzzle, pinnae, and/or periorbital area) were present at 12 mg/kg/day. • Decreased body weights were seen in males and females at ≥ 4 and 12 mg/kg/day, respectively. • Decreased mean spermatozoa counts and mean cauda epididymis weights occurred at 12 mg/kg/day without corresponding microscopic findings or effects on reproductive performance. • Decreased fetal weights and reduced ossification occurred

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
				at 12 mg/kg/day. • Increased incidence of fetuses with rudimentary 14th ribs (with and without contralateral ossification centers) occurred at ≥ 4 mg/kg/day and was considered a result of differences in the rates of ossification, and not of teratological significance.
Fertility and Developmental Toxicity RPT-42298 (cont'd)				• Increased incidence of fetuses, but not litters, with minor skeletal anomalies at 12 mg/kg/day. • Parental NTELs were considered to be 1 and 4 mg/kg/day for males and females, respectively; and the fetal NTEL was considered to be 4 mg/kg/day. • Mean values for dosages 1, 4, and 12 mg/kg/day, respectively were: GD 6: C_{5min} (µg/mL):0.97, 4.6, 21 AUC_{0-24}(µg•h/mL): 1.79, 7.07, 24.8 GD 17: C_{5min} (µg/mL): 1.78, 10.7, 24.0 AUC_{0-24} (µg•h/mL): 2.30, 11.3, 28.5.
Perinatal/ Postnatal Toxicity RPT-53525	Rats; S-D; 25F/dosage; 11 weeks; 235 – 296 g	IV, bolus (needle); once daily from GD 6 through day 20 postpartum	0 (0 mg/mL), 1 (1 mg/mL), 4 (4 mg/mL), 12 (12 mg/mL); 1 mL/kg; pH of the dosing solutions ranged from 6.68 to 7.95	• Maternal evaluations were based on mortality, clinical observations, body weight, food consumption, and parturition parameters. Offspring evaluations were based on mortality, clinical observations, body weight, developmental parameters, and reproductive capabilities. • No effects on pregnancy (F0), offspring survival, growth, and development (physical, sensory, behavioral, and reproductive) at dosages producing maternal toxicity (≥ 4 mg/kg/day). • Maternal (F0) body-weight gain and food consumption were

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
				decreased during gestation at ≥ 4 mg/kg/day. • Maternal NOAEL was considered to be 1 mg/kg/day; fetal and offspring (F1 and generation) development NOAEL was considered to be 12 mg/kg/day.
Dose-Ranging Developmental Toxicity GTR-33215	Rabbits; NZW 8F/dosage, 4F/dosage for TK; 5 - 6 months; 2.9 – 4.1 kg;	IV, bolus (needle); once daily from GD 6 through GD 18	0 (0 mg/mL), 1 (1 mg/mL), 4 (4 mg/mL), 16 (16 mg/mL); 1 mL/kg;	• Maternal evaluations were based on mortality, clinical observations, abortion rate, body weight, food consumption, gravid uterine weight, hysterotomy findings, TK, and postmortem examinations. Fetal evaluations were based on weight, and gross external and palatal examinations. • There was no tigecycline-related mortality. • Clinical observations consisted of fecal alterations (no feces or diarrhea/loose feces) at all dosages, and 3 animals aborted at 16 mg/kg/day. • Maternal body weight and body-weight gain were affected at ≥ 4 mg/kg/day. At 16 mg/kg/day, a mean body-weight loss of 17% compared with pretest weight was observed at the end of the dosing period. • Food consumption at 4 mg/kg/day was decreased 39% compared with controls at the end of the dosing period. At 16 mg/kg/day, food consumption was markedly decreased (99% by the end of the dosing period), with some animals consuming only a few grams per day. Partial recovery was generally seen in both body-weight gain and food consumption after the cessation of dosing. • Gravid uterine weights were decreased 24% and 74% at 4 and 16 mg/kg/day, respectively, compared with controls. • There was an increased incidence of resorptions at 4 and 16 mg/kg/day compared with controls. The postimplantation loss was 9% and 50% at 4 and 16 mg/kg/day, respectively,

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
Dose-Ranging Developmental Toxicity GTR-33215 (cont'd)				compared with 0% at 1 mg/kg/day and in the vehicle-control group. Consequently, the number of viable fetuses was decreased by 15% and 55% at 4 and 16 mg/kg/day, respectively. Fetal weights were decreased by 13% and 53% at 4 and 16 mg/kg/day, respectively. There were no tigecycline-related fetal gross anomalies at any dosage. • On GD 18, AUC_{0-24} values increased in a greater than proportional manner with increasing dosage; particularly between 4 and 16 mg/kg/day. Mean tigecycline values for dosages 1, 4, and 16 mg/kg/day were, respectively: GD 18: C_{5min} (µg/mL): 1.05, 8.69, 122 AUC_{0-24} (µg•h/mL): 0.98, 7.45, 93.5. • The maternal and fetal NTELs in this study were considered to be 1 mg/kg/day.
Developmental Toxicity RPT-42304	Rabbits; NZW 20F/dosage; ~ 5 months; 3.0 – 3.5 kg	IV, bolus (needle); once daily from GD 6 through GD 18	0 (0 mg/mL), 0.25 (0.25 mg/mL), 1 (1 mg/mL), 4 (4 mg/mL); 1 mL/kg; pH of the dosing solutions ranged from 7.53 to 7.97	• Maternal evaluations were based on mortality, clinical observations, abortion rate, body weight, food consumption, gravid uterine weight, hysterotomy findings, TK, and postmortem examinations. Fetal evaluations were based on gender, weight, and gross external, visceral, and skeletal examinations. • Not teratogenic. • Abortion, clinical signs (fecal alterations), and body weight loss and decreased food consumption occurred at 4 mg/kg/day in maternal animals compared with controls. • Fetal weights at 4 mg/kg/day were slightly lower (8.3%) than controls. • Increased percentage of fetuses with semi-bipartite thoracic

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
				vertebral centra and unilateral and/or bilateral 13th ribs (considered indicative of differences in ossification and not teratologically significant) occurred at 4 mg/kg/day.
Developmental Toxicity RPT-42304 (cont'd)				• In this study the maternal NTEL was considered to be 1.0 mg/kg/day and the NTEL for developmental toxicity was considered to be 4.0 mg/kg/day. • Mean tigecycline values for dosages 0.25, 1, and 4 mg/kg/day were, respectively: GD 6: C_{5min} (µg/mL): 0.289, 1.03, 10.2 AUC_{0-24} (µg•h/mL): 0.220, 1.49, 9.69 GD 18: C_{5min} (µg/mL): 0.318, 1.26, 6.30 AUC_{0-24} (µg•h/mL): 0.206, 1.29, 6.75.
Other Toxicity Studies				
Antigenicity GTR-33263	Sensitization: Mice; BALB/c and C3H/He; 6F/strain/dose group 7 – 9 weeks; 14 – 22 g	IV, bolus (needle) or IP; once a week for 3 weeks	0 (0 mg/mL), 3 (3 mg/mL), 30 (30 mg/mL); 10 mL/kg; pH of the dosing solutions ranged from 7.18 to 8.29	• Evaluations were based on clinical observations, body weight, Passive Cutaneous Anaphylaxis (PCA) assay and measurement of histamine levels. • Not antigenic as assessed by PCA assay. • Serum histamine levels in rats 10 to 15 minutes after 30 mg/kg IV dose were not biologically significantly increased.
	Challenge: Rats; S-D 2F/serum sample, 6F;	IV, bolus; 1 day	30; 1 mL/kg	

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
	10 weeks; 177- 253 g			
Antigenicity GTR-33124	Guinea Pig; Hartley; 4M/group 5 weeks; 299 – 455 g	IV, bolus (needle) or SC; 1 day	0.3 (0,3 mg/mL), 1 (1 mg/mL), 3 (3 mg/mL); 1 mL/kg; pH of the dosing solutions ranged from 7.15 to 7.81	• Evaluations were based on mortality, clinical observations, body weight, and measurement of histamine levels. • After IV administration of 3 mg/kg, adverse tigecycline-related clinical signs were twitching, respiratory alterations, erythema, blue extremities. • Recovery was evident at 24 hours. • All other animals appeared normal at every observation period. • Serum histamine levels at 10 to 15 minutes post dose were not increased in available samples (0.3 and 1 mg/mL). • The intolerability observed in this study precluded further studies in this species.
Hematotoxicity Recoverability GTR-33279	Dogs; Beagle 3/sex/dosage; ~ 11 months; 9.3 – 11.8 kg (males), 7.7 – 12.3 kg (females)	IV, bolus (needle); once daily for 2 weeks with a 3-week recovery	0 (0 mg/mL), 12 (6 mg/mL); 2 mL/kg; pH of the dosing solution ranged from 7.0 to 8.0	• Evaluations were based on mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry and urinalysis. • Hematotoxicity of tigecycline was characterized by decreases in RBC parameters, reticulocytes, WBCs, and platelets. • Tigecycline-related clinical signs (including erythema, swollen areas, animal appearing itchy after dosing, red discoloration of the sclera, lacrimation, emesis, and fecal alterations) occurred in dogs given 12 mg/kg/day. • Slight to moderate (10% to 17 %) body-weight loss. • Increased APTT (up to 86 %) was present in tigecycline treated dogs. • Recovery in all evaluated parameters was evident by the

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
				end of a 3-week tigecycline-free period in all tigecycline-treated dogs. • No irreversible tigecycline-related hematotoxicity was evident.
Phototoxicity Assessment RPT-55059	Male Rats; Long-Evans; 5M/dosage; ~ 8 weeks; 263 – 284 g	IV, bolus (needle); single dose UVR exposure: 30 min (½ MED) to eyes and skin at 5 and 120 minutes post-dose	0 (0 mg/mL), 10 (10 mg/mL), 30 (30 mg/mL), 70 (70 mg/mL); 1 mL/kg; pH of the dosing solutions ranged from 7.8 to 7.9	• Evaluations were based on mortality, clinical observations, body weight, ophthalmoscopy, and microscopic ocular examinations • Animals were observed up to 3 days post-dose • After IV administration, both dermal and ocular assessments were negative for phototoxicity. • No adverse tigecycline-related clinical signs, body weight, ophthalmoscopic abnormalities or microscopic ocular findings.
Emetogenic Potential RPT-39987	*Suncus murinus;* 2, 3, or 4/dosage *Suncus murinus;* 3/dosage	IV, infusion (catheter); single dose Oral; single dose	0, 100, 300, 600; 10 mL/kg; 1 mL/min; 0, 300, 600, 1000; 10 mL/kg; distilled water	• Evaluations were based on mortality and emesis. • After IV administration, emesis was induced only at a lethal dosage (600 mg/kg). • After oral administration, emesis was induced at 600 and 1000 mg/kg, but not at 300 mg/kg.
In Vitro Blood Compatibility GTR-32502	Rat, Dog, and Human Blood	*In Vitro*	70 mg/mL (rat) 20 mg/mL (dog) 8 mg/mL (human); NA	• Not hemolytic. • The upper limit for valid rat blood test results was 35 mg/mL; 8 % hemolysis in human blood at 8 mg/mL; 24 % protein precipitation in dog plasma at 20 mg/mL. • No other hemolysis or protein precipitation was observed in this study. • Tigecycline solutions of 35, 20, and 8 mg/mL were compatible with rat, dog, and human blood, with levels of

Type of Study	Species; Strain[b]; N; Age; Weight	Route[c]; Duration	Dosage[a] (Concentration); Dosing Volume or Infusion Rate; Vehicle[d]	Principal Effects Observed
				hemolysis and/or protein precipitation not considered to be toxicologically significant.
Cellular Protein Synthesis and Mitochondrial Protein Synthesis MIRACL-26519	Dog Hepatocytes Rat and Dog Mitochondrial Suspensions	*In Vitro*	1 to 100 µg/mL; 20 hours 9.4 to 282 µg/mL; 1 hour	• Did not inhibit cellular protein synthesis. • Inhibited mitochondrial protein synthesis in preparations in a dose dependent manner (up to 43% and 85% inhibition in the dog and rat, respectively compared to control).

a. Dosage in mg/kg/day for repeat-dose studies, as appropriate, unless otherwise indicated.
b. Includes males and females unless otherwise indicated.
c. IV bolus unless otherwise indicated.
d. The vehicle was 0.9% saline, unless otherwise noted.
e. Dosages are expressed in the report as 45, 90, or 180 mg/kg/day of the monohydrochloride salt of tigecycline.
f. The NTEL is underlined for the 2- and 13-week pivotal studies in rats, 2-week pivotal study in dogs, and 13-week pivotal study in dogs (also NOAEL).

Note:
In the studies summarized in Table 19, tigecycline was administered as the free base, as the monohydrochloride salt, or as the dihydrochloride salt.
Unless otherwise noted in the table, the approximate pH of the dosing solution was not tested

ALT = Alanine aminotransferase; AUC = Area under the concentration-versus-time curve; BUN = Blood urea nitrogen; CD = Cesarean-derived; CHO = Chinese hamster ovary; F = Females, F_0 = Parental; GD = Gestation day; GI = Gastrointestinal; IP = Intraperitoneal; IV = Intravenous; LD_{50} = Median lethal dosage; M = Males, MPV = Mean platelet volume; NA = Not applicable; NOAEL = No-observed-adverse-effect level; NTEL = No-toxicologic-effect level; NZW = New Zealand White; RBC = Red blood cell; SC = Subcutaneous; S-D = Sprague-Dawley; TK = Toxicokinetics; WBC = White blood cell.

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15. Product Monograph - ^{PR}TYGACIL (Tigecycline for Injection) 50 mg/vial (Pfizer Canada Inc.) Date of Revision: 6 December 2012.

PART III: CONSUMER INFORMATION

PrTIGECYCLINE
Tigecycline for Injection

This leaflet is part III of a three-part "Product Monograph" published when TIGECYCLINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TIGECYCLINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
The name of the medicine you have been given is TIGECYCLINE. Your doctor prescribed TIGECYCLINE because you have one of the following types of serious infections:

Complicated bacterial infection of the skin
Complicated bacterial infection in the abdomen
Mild to moderate community acquired pneumonia (lung infection caught outside of a hospital)

TIGECYCLINE is for use in patients 18 years of age and over.

What it does:
TIGECYCLINE is an antibiotic that works by helping to stop the growth of bacteria that cause infections.

When it should not be used:
Do not use TIGECYCLINE if you are allergic to tigecycline or tetracycline antibiotics.

What the medicinal ingredient is:
Tigecycline

What the important nonmedicinal ingredients are:
Lactose monohydrate.

What dosage forms it comes in:
TIGECYCLINE for Injection is supplied in a single-dose 5 mL glass vial containing lyophilized powder for reconstitution, and is an orange cake or powder.

WARNINGS AND PRECAUTIONS

If you develop any allergic reaction, (e.g. rash, difficulty in breathing, tightening of chest, swelling of lips, tongue or throat, etc.), tell your doctor or nurse immediately.

If you develop severe diarrhea, tell your doctor or nurse immediately. Do this even if it occurs several weeks after TIGECYCLINE has been stopped. Diarrhea may mean that you have a serious condition affecting your bowel. You may need urgent Medical care. Do not take any diarrhea medicine without first checking with your doctor.

BEFORE you use TIGECYCLINE talk to your doctor or pharmacist if:

- **You have bowel problems**
  While using antibiotics or after finishing them, you experience severe abdominal or stomach cramps, or watery and severe diarrhea.

- **You have other infections**
  While antibiotics including TIGECYCLINE fight certain bacteria, other bacteria and fungi may continue to grow. This is called overgrowth. Your doctor will monitor you for any potential infections and treat you if necessary.

- **You are pregnant**
  TIGECYCLINE may cause fetal harm. If you are pregnant, or are planning to become pregnant, talk to your doctor before receiving TIGECYCLINE.

- **You are breast-feeding**
  It is not known if TIGECYCLINE passes into breast milk. Ask your doctor for advice before breastfeeding your baby.

- **You have liver problems**
  You should inform your doctor if you have or had liver disease. Depending on the condition of your liver, your doctor may reduce the dose to avoid potential side effects.

- **You are driving and using machines**
  TIGECYCLINE may cause side effects such as dizziness. This may impair your ability to drive or operate machinery.

- **Children**
  TIGECYCLINE is not recommended in children because there is no experience with the use of TIGECYCLINE in patients under 18 years of age.

  TIGECYCLINE, which is similar in structure to tetracycline antibiotics, may cause enamel loss and staining in developing teeth.

While Taking TIGECYCLINE:

- If you develop a racing heartbeat (palpitations) or faint while using TIGECYCLINE, contact your doctor immediately.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with TIGECYCLINE include:

Always tell your doctor if you are taking warfarin or any other medicines, including medicines you buy without a prescription.

TIGECYCLINE may interfere with the contraceptive pill (birth control pill). Talk to your doctor about the need for an additional method of contraception while receiving TIGECYCLINE.

PROPER USE OF THIS MEDICATION

Usual adult dose:
TIGECYCLINE is given intravenously (into a vein) and administered to you by your doctor or nurse.

The recommended dose is 100 mg given initially, followed by 50mg every 12 hours, given by intravenous infusion over a period of 30-60 minutes.

It is very important that you continue to receive TIGECYCLINE for as long as your doctor prescribes it. Your doctor will decide how many days of treatment you need.

Overdose:
If you are concerned that you may have been given too much TIGECYCLINE, talk to your doctor or nurse immediately.

Missed Dose:
If you are concerned that you may have missed a dose, talk to your doctor or nurse immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, TIGECYCLINE may have side effects.
The most common side effects are:

- Nausea
- Vomiting
- Diarrhea
- Abdominal pain
- Dizziness
- Skin rash
- Itching
- Headache
- Abdominal discomfort

Tigecycline may cause drowsiness. Do not drive a car or operate machinery until you know how to react to Tigecycline

Less common side effects are:

- Injection site reaction (pain, redness, inflammation)
- Vein irritations from the injection including pain, inflammation, swelling and clotting.
- Fever
- Chills
- chest pain
- Jaundice (yellowness of skin or eye)
- Allergic reaction (e.g. rash, difficulty in breathing, tightening of chest, swelling of lips, tongue or throat, etc.)

If these become bothersome, contact your doctor

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common				
Uncommon	• Injection site reaction		√	
	• Vein irritations		√	
	• Difficulty in breathing		√	
	• Fever		√	
	• Chills		√	
	• Chest pain		√	
	• Jaundice		√	
	• Allergic reaction		√	

This is not a complete list of side effects. For any unexpected effects while taking TIGECYCLINE, contact your doctor or pharmacist.

HOW TO STORE IT

TIGECYCLINE powder should be stored at a Controlled Room Temperature 20°C to 25°C (68°-77°F), excursions permitted to 15°C - 30°C (59°-86°F). TIGECYCLINE must be kept out of the reach and sight of children. TIGECYCLINE will be given to you only within the "use-by" date of the product.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Apotex Inc. at 1-800-667-4708 or visit the www.apotex.ca.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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