FRESENIUS KABI

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Tigecycline
for Injection, USP

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TIGECYCLINE FOR INJECTION safely and effectively. See full prescribing information for TIGECYCLINE FOR INJECTION.

TIGECYCLINE for injection, for intravenous use
Initial U.S. Approval: 2005

WARNING: ALL-CAUSE MORTALITY
See full prescribing information for complete boxed warning.

All-cause mortality was higher in patients treated with tigecycline for injection than comparators in a meta-analysis of clinical trials. The cause of this mortality risk difference of 0.6% (95% CI 0.1, 1.2) has not been established. Tigecycline for injection should be reserved for use in situations when alternative treatments are not suitable *(1.4, 5.1, 5.2, 6.1).*

INDICATIONS AND USAGE

Tigecycline for injection is a tetracycline class antibacterial indicated in patients 18 years of age and older for:
- Complicated skin and skin structure infections (1.1)
- Complicated intra-abdominal infections (1.2)
- Community-acquired bacterial pneumonia (1.3)

Limitations of Use: Tigecycline for injection is not indicated for treatment of diabetic foot infection or hospital-acquired pneumonia, including ventilator-associated pneumonia. (1.4)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of tigecycline for injection and other antibacterial drugs, tigecycline for injection should be used only to treat infections that are proven or strongly suspected to be caused by bacteria. (1.5)

DOSAGE AND ADMINISTRATION

- Initial dose of 100 mg, followed by 50 mg every 12 hours administered intravenously over approximately 30 to 60 minutes. (2.1)
- Severe hepatic impairment (Child Pugh C): Initial dose of 100 mg followed by 25 mg every 12 hours. (2.2)

DOSAGE FORMS AND STRENGTHS

For Injection: 50 mg, lyophilized powder for reconstitution in a single dose 10 mL vial. (3)

CONTRAINDICATIONS

Known hypersensitivity to tigecycline. (4)

WARNINGS AND PRECAUTIONS

- All-Cause Mortality: A meta-analysis of Phase 3 and 4 clinical trials demonstrated an increase in all-cause mortality in tigecycline-treated patients compared to controls with a risk difference of 0.6% (95% CI 0.1, 1.2). The cause of this increase has not been established. An increase was also seen in a meta-analysis limited to the approved indications [0.6% (95% CI 0, 1.2)]. The greatest difference in mortality was seen in tigecycline-treated patients with ventilator-associated pneumonia. (5.1, 5.2)
- Anaphylactic Reactions: have been reported with tigecycline, and may be life-threatening. Avoid use in patients with known hypersensitivity to tetracyclines. (5.3)
- Hepatic Adverse Effects: have been reported 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. (5.4)
- Pancreatitis: including fatalities, has been reported with tigecycline. If pancreatitis is suspected, then consider stopping tigecycline. (5.5)
- Fetal Harm: Tigecycline may cause fetal harm when administered to a pregnant woman. (5.6)
- Tooth Discoloration: The use of tigecycline during tooth development may cause permanent discoloration of the teeth. (5.7)
- *Clostridium difficile*-Associated Diarrhea (CDAD): evaluate if diarrhea occurs. (5.8)

ADVERSE REACTIONS

The most common adverse reactions (incidence > 5%) are nausea, vomiting, diarrhea, abdominal pain, headache, and increased SGPT. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Suitable anticoagulation test should be monitored if tigecycline is administered to patients receiving warfarin. (7.1)

USE IN SPECIFIC POPULATIONS

Pediatrics: Use in patients under 18 years of age is not recommended. Pediatric trials were not conducted because of the higher risk of mortality seen in adult trials. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 01/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ALL-CAUSE MORTALITY

An increase in all-cause mortality has been observed in a meta-analysis of Phase 3 and 4 clinical trials in tigecycline-treated patients versus comparator. The cause of this mortality risk difference of 0.6% (95% CI 0.1, 1.2) has not been established. Tigecycline should be reserved for use in situations when alternative treatments are not suitable *[see Indications and Usage (1.4), Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)].*

1 INDICATIONS AND USAGE

1.1 Complicated Skin and Skin Structure Infections

Tigecycline for injection is indicated in patients 18 years of age and older for the treatment of complicated skin and skin structure infections caused by susceptible isolates of *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae, Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Streptococcus pyogenes, Enterobacter cloacae, Klebsiella pneumoniae,* and *Bacteroides fragilis.*

1.2 Complicated Intra-abdominal Infections

Tigecycline for injection is indicated in patients 18 years of age and older for the treatment of complicated intra-abdominal infections caused by susceptible isolates of *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens,* and *Peptostreptococcus micros.*

1.3 Community-Acquired Bacterial Pneumonia

Tigecycline for injection is indicated in patients 18 years of age and older for the treatment of community-acquired bacterial pneumonia caused by susceptible isolates of *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae*, and *Legionella pneumophila*.

1.4 Limitations of Use

Tigecycline for injection is not indicated for the treatment of diabetic foot infections. A clinical trial failed to demonstrate non-inferiority of tigecycline for injection for treatment of diabetic foot infections.

Tigecycline for injection is not indicated for the treatment of hospital-acquired or ventilator-associated pneumonia. In a comparative clinical trial, greater mortality and decreased efficacy were reported in tigecycline-treated patients *[see Warnings and Precautions (5.2)]*.

1.5 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of tigecycline and other antibacterial drugs, tigecycline for injection should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to tigecycline. Tigecycline for injection may be initiated as empiric monotherapy before results of these tests are known.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Adult Dosage

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

The recommended duration of treatment with tigecycline for injection for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days. The recommended duration of treatment with tigecycline for injection for community-acquired bacterial pneumonia is 7 to 14 days. The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress.

2.2 Dosage in Patients with Hepatic Impairment

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline for injection should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response *[see Clinical Pharmacology (12.3) and Use in Specific Populations (8.6)]*.

2.3 Dosage in Pediatric Patients

The safety and efficacy of the proposed pediatric dosing regimens have not been evaluated due to the observed increase in mortality associated with tigecycline in adult patients. Avoid use of tigecycline in pediatric patients unless no alternative antibacterial drugs are available. Under these circumstances, the following doses are suggested:

- Pediatric patients aged 8 to 11 years should receive 1.2 mg/kg of tigecycline every 12 hours intravenously to a maximum dose of 50 mg of tigecycline every 12 hours.
- Pediatric patients aged 12 to 17 years should receive 50 mg of tigecycline every 12 hours.

The proposed pediatric doses of tigecycline were chosen based on exposures observed in pharmacokinetic trials, which included small numbers of pediatric patients *[see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]*.

There are no data to provide dosing recommendations in pediatric patients with hepatic impairment.

2.4 Preparation and Administration

Each vial of tigecycline for injection should be reconstituted with 5.3 mL of 0.9% Sodium Chloride Injection, USP, 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. Reconstituted solution must be transferred and further diluted for intravenous infusion. Withdraw 5 mL of the reconstituted solution from the vial and add to a 100 mL intravenous bag for infusion (for a 100 mg dose, reconstitute two vials; for a 50 mg dose, reconstitute one vial). The maximum concentration in the intravenous 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. Once reconstituted, tigecycline for injection 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 intravenous bag). If the storage conditions exceed 25°C (77°F) after reconstitution, tigecycline should be used immediately. Alternatively, tigecycline for injection mixed with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP may be stored refrigerated at 2° to 8°C (36° to 46°F) for up to 48 hours following immediate transfer of the reconstituted solution into the intravenous bag.

Tigecycline for injection 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 for injection with 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP or Lactated Ringer's Injection, USP. Injection should be made with an infusion solution compatible with tigecycline and with any other drug(s) administered via this common line.

2.5 Drug Compatibilities

Compatible intravenous solutions include 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, and Lactated Ringer's Injection, USP. When administered through a Y-site, tigecycline for injection is compatible with the following drugs or diluents when used with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP: amikacin, dobutamine, dopamine HCl, gentamicin, Lactated Ringer's, lidocaine HCl, metoclopramide, morphine, norepinephrine, potassium chloride, propofol (tested with 5% Dextrose Injection, USP only), ranitidine HCl, theophylline, and tobramycin.

2.6 Drug Incompatibilities

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

3 DOSAGE FORMS AND STRENGTHS

For Injection: Each single dose 10 mL glass vial contains 50 mg of tigecycline for injection, USP as an orange lyophilized powder for reconstitution.

4 CONTRAINDICATIONS

Tigecycline for injection is contraindicated for use in patients who have known hypersensitivity to tigecycline. Reactions have included anaphylactic reactions *[see Warnings and Precautions (5.3) and Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 All-Cause Mortality

An increase in all-cause mortality has been observed in a meta-analysis of Phase 3 and 4 clinical trials in tigecycline-treated patients versus comparator-treated patients. In all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3,788) of patients receiving tigecycline and 3.0% (110/3,646) of patients receiving comparator drugs. In a pooled analysis of these trials, based on a random effects model by trial weight, the adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1, 1.2) between tigecycline and comparator-treated patients. An analysis of mortality in all trials conducted for approved indications (cSSSI, cIAI, and CABP), including post-market trials showed an adjusted mortality rate of 2.5% (66/2,640) for tigecycline and 1.8% (48/2,628) for comparator, respectively. The adjusted risk difference for mortality stratified by trial weight was 0.6% (95% CI 0.0, 1.2).

The cause of this mortality difference has not been established. Generally, deaths were the result of worsening infection, complications of infection or underlying co-morbidities. Tigecycline should be reserved for use in situations when alternative treatments are not suitable *[see Boxed Warning, Indications and Usage (1.4), Warnings and Precautions (5.2) and Adverse Reactions (6.1)].*

5.2 Mortality Imbalance and Lower Cure Rates in Hospital-Acquired Pneumonia

A trial of patients with hospital acquired, including ventilator-associated, pneumonia failed to demonstrate the efficacy of tigecycline. In this trial, patients were randomized to receive tigecycline (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. 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).

In this trial, greater mortality was seen in patients with ventilator-associated pneumonia who received tigecycline (25/131 [19.1%] versus 15/122 [12.3%] in comparator-treated patients) *[see Adverse Reactions (6.1)]*. Particularly high mortality was seen among tigecycline-treated patients with ventilator-associated pneumonia and bacteremia at baseline (9/18 [50.0%] versus 1/13 [7.7%] in comparator-treated patients).

5.3 Anaphylactic Reactions

Anaphylactic reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening. Tigecycline is structurally similar to tetracycline-class antibiotics and should be avoided in patients with known hypersensitivity to tetracycline-class antibiotics.

5.4 Hepatic Adverse Effects

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 being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. 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. Hepatic dysfunction may occur after the drug has been discontinued.

5.5 Pancreatitis

Acute pancreatitis, including fatal cases, has occurred in association with tigecycline treatment. 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 *[see Adverse Reactions (6.2)]*.

5.6 Fetal Harm

Tigecycline may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking tigecycline, the patient should be apprised of the potential hazard to the fetus. Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. Decreased fetal weights in rats and rabbits (with associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline *[see Use in Specific Populations (8.1)]*.

5.7 Tooth Discoloration

The use of tigecycline during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Results of studies in rats with tigecycline have shown bone discoloration. Tigecycline should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.

5.8 *Clostridium difficile* Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including tigecycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.9 Sepsis/Septic Shock in Patients with Intestinal Perforation

Monotherapy with tigecycline should be avoided in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In cIAI studies (n=1,642), 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) versus 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.

5.10 Tetracycline-Class Adverse Effects

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

5.11 Development of Drug-Resistant Bacteria

Prescribing tigecycline for injection in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- All-Cause Mortality *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Mortality Imbalance and Lower Cure Rates in Hospital-Acquired Pneumonia *[see Warnings and Precautions (5.2)]*
- Anaphylaxis *[Warning and Precautions (5.3)]*
- Hepatic Adverse Effects *[Warnings and Precautions (5.4)]*
- Pancreatitis *[Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, 2,514 patients were treated with tigecycline. Tigecycline was discontinued due to adverse reactions in 7% of patients compared to 6% for all comparators. Table 1 shows the incidence of adverse reactions through test of cure reported in ≥ 2% of patients in these trials.

Table 1. Incidence (%) of Adverse Reactions Through Test of Cure Reported in ≥ 2% of Patients Treated in Clinical Studies

Body System Adverse Reactions	Tigecycline (N=2,514)	Comparators[a] (N=2,307)
Body as a Whole		
Abdominal pain	6	4
Abscess	2	2
Asthenia	3	2
Headache	6	7
Infection	7	5
Cardiovascular System		
Phlebitis	3	4
Digestive System		
Diarrhea	12	11
Dyspepsia	2	2
Nausea	26	13
Vomiting	18	9
Hemic and Lymphatic System		
Anemia	5	6
Metabolic and Nutritional		
Alkaline Phosphatase Increased	3	3
Amylase Increased	3	2
Bilirubinemia	2	1
BUN Increased	3	1
Healing Abnormal	3	2
Hyponatremia	2	1
Hypoproteinemia	5	3
SGOT Increased[b]	4	5
SGPT Increased[b]	5	5
Respiratory System		
Pneumonia	2	2
Nervous System		
Dizziness	3	3
Skin and Appendages		
Rash	3	4

[a] Vancomycin/Aztreonam, Imipenem/Cilastatin, Levofloxacin, Linezolid.
[b] LFT abnormalities in tigecycline-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.

In all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3,788) of patients receiving tigecycline and 3.0% (110/3,646) 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 (see Table 2). The cause of the imbalance has not been established. Generally, deaths were the result of worsening infection, complications of infection or underlying co-morbidities.

Table 2. Patients with Outcome of Death by Infection Type

	Tigecycline		Comparator		Risk Difference*
Infection Type	n/N	%	n/N	%	% (95% CI)
cSSSI	12/834	1.4	6/813	0.7	0.7 (-0.3, 1.7)
cIAI	42/1,382	3.0	31/1,393	2.2	0.8 (-0.4, 2)
CAP	12/424	2.8	11/422	2.6	0.2 (-2, 2.4)
HAP	66/467	14.1	57/467	12.2	1.9 (-2.4, 6.3)
Non-VAP[a]	41/336	12.2	42/345	12.2	0.0 (-4.9, 4.9)
VAP[a]	25/131	19.1	15/122	12.3	6.8 (-2.1, 15.7)
RP	11/128	8.6	2/43	4.7	3.9 (-4, 11.9)
DFI	7/553	1.3	3/508	0.6	0.7 (-0.5, 1.8)
Overall Adjusted	150/3,788	4.0	110/3,646	3.0	0.6 (0.1, 1.2)**

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections;
cSSSI = Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia;
VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infections.
* The difference between the percentage of patients who died in tigecycline and comparator treatment groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.
** Overall adjusted (random effects model by trial weight) risk difference estimate and 95% CI.
[a] These are subgroups of the HAP population.
Note: The 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 and without osteomyelitis).

An analysis of mortality in all trials conducted for approved indications - cSSSI, cIAI, and CABP, including post-market trials (one in cSSSI and two in cIAI) - showed an adjusted mortality rate of 2.5% (66/2,640) for tigecycline and 1.8% (48/2,628) for comparator, respectively. The adjusted risk difference for mortality stratified by trial weight was 0.6% (95% CI 0.0, 1.2).

In comparative clinical studies, infection-related serious adverse reactions were more frequently reported for subjects treated with tigecycline (7%) versus comparators (6%). Serious adverse reactions of sepsis/septic shock were more frequently reported for subjects treated with tigecycline (2%) versus comparators (1%). 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 (5.9)]*.

The most common adverse reactions were nausea and vomiting which generally occurred during the first 1 to 2 days of therapy. The majority of cases of nausea and vomiting associated with tigecycline and comparators were either mild or moderate in severity. In patients treated with tigecycline, nausea incidence was 26% (17% mild, 8% moderate, 1% severe) and vomiting incidence was 18% (11% mild, 6% moderate, 1% severe).

In patients treated for complicated skin and skin structure infections (cSSSI), nausea incidence was 35% for tigecycline and 9% for vancomycin/aztreonam; vomiting incidence was 20% for tigecycline and 4% for vancomycin/aztreonam. In patients treated for complicated intra-abdominal infections (cIAI), nausea incidence was 25% for tigecycline and 21% for imipenem/cilastatin; vomiting incidence was 20% for tigecycline and 15% for imipenem/cilastatin. In patients treated for community-acquired bacterial pneumonia (CABP), nausea incidence was 24% for tigecycline and 8% for levofloxacin; vomiting incidence was 16% for tigecycline and 6% for levofloxacin.

Discontinuation from tigecycline was most frequently associated with nausea (1%) and vomiting (1%). For comparators, discontinuation was most frequently associated with nausea (< 1%).

The following adverse reactions were reported (< 2%) in patients receiving tigecycline in clinical studies:

Body as a Whole: injection site inflammation, injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis

Cardiovascular System: thrombophlebitis

Digestive System: anorexia, jaundice, abnormal stools

Metabolic/Nutritional System: increased creatinine, hypocalcemia, hypoglycemia

Special Senses: taste perversion

Hemic and Lymphatic System: partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia, increased international normalized ratio (INR), thrombocytopenia

Skin and Appendages: pruritus

Urogenital System: vaginal moniliasis, vaginitis, leukorrhea

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of tigecycline. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure.

- anaphylactic reactions
- acute pancreatitis
- hepatic cholestasis, and jaundice
- severe skin reactions, including Stevens-Johnson Syndrome
- symptomatic hypoglycemia in patients with and without diabetes mellitus

7 DRUG INTERACTIONS

7.1 Warfarin

Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin *[see Clinical Pharmacology (12.3)]*.

7.2 Oral Contraceptives

Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects—Pregnancy Category D *[see Warnings and Precautions (5.6)]*

Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, ^{14}C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of tigecycline was associated with reductions in fetal weights and an increased incidence of skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively (28 mcg•hr/mL and 6 mcg•hr/mL at 12 and 4 mg/kg/day). An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.

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

8.3 Nursing Mothers

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

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tigecycline is administered to a nursing woman *[see Warnings and Precautions (5.7)]*.

8.4 Pediatric Use

Use in patients under 18 years of age is not recommended. Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Because of the increased mortality observed in tigecycline-treated adult patients in clinical trials, pediatric trials of tigecycline to evaluate the safety and efficacy of tigecycline were not conducted.

In situations where there are no other alternative antibacterial drugs, dosing has been proposed for pediatric patients 8 to 17 years of age based on data from pediatric pharmacokinetic studies *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

Because of effects on tooth development, use in patients under 8 years of age is not recommended *[see Warnings and Precautions (5.7)]*.

8.5 Geriatric Use

Of the total number of subjects who received tigecycline in Phase 3 clinical studies (n=2,514), 664 were 65 and over, while 288 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

No significant difference in tigecycline exposure was observed between healthy elderly subjects and younger subjects following a single 100 mg dose of tigecycline *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.2)]*.

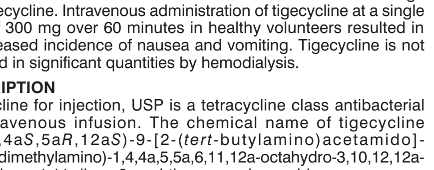
10 OVERDOSAGE

No specific information is available on the treatment of overdosage with tigecycline. Intravenous administration of tigecycline at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. Tigecycline is not removed in significant quantities by hemodialysis.

11 DESCRIPTION

Tigecycline for injection, USP is a tetracycline class antibacterial for intravenous infusion. The chemical name of tigecycline is (4*S*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

The following represents the chemical structure of tigecycline:



$C_{29}H_{39}N_5O_8$ M.W. 585.65

Figure 1: Structure of Tigecycline

Tigecycline for injection, USP is an orange lyophilized powder or cake. Each tigecycline single dose 10 mL vial contains 50 mg tigecycline and 82.6 mg of arginine as lyophilized powder for reconstitution for intravenous infusion. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide. The product does not contain preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tigecycline is a tetracycline class antibacterial *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

The mean pharmacokinetic parameters of tigecycline after single and multiple intravenous doses based on pooled data from clinical pharmacology studies 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 Dose 100 mg (N=224)	Multiple Dose[a] 50 mg every 12h (N=103)
C_{max} (mcg/mL)[b]	1.45 (22%)	0.87 (27%)
C_{max} (mcg/mL)[c]	0.90 (30%)	0.63 (15%)
AUC (mcg•h/mL)	5.19 (36%)	- -
AUC_{0-24h} (mcg•h/mL)	- -	4.7 (36%)
C_{min} (mcg/mL)	- -	0.13 (59%)
$t_{½}$ (h)	27.1 (53%)	42.4 (83%)
CL (L/h)	21.8 (40%)	23.8 (33%)
CL_r (mL/min)	38.0 (82%)	51.0 (58%)
V_{ss} (L)	568 (43%)	639 (48%)

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] 30-minute infusion
[c] 60-minute infusion

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 mcg/mL). 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.

Following the administration of tigecycline 100 mg followed by 50 mg every 12 hours to 33 healthy volunteers, the tigecycline AUC_{0-12h} (134 mcg•h/mL) in alveolar cells was approximately 78-fold higher than the AUC_{0-12h} in the serum, and the AUC_{0-12h} (2.28 mcg•h/mL) in epithelial lining fluid was approximately 32% higher than the AUC_{0-12h} in serum. The AUC_{0-12h} (1.61 mcg•h/mL) of tigecycline in skin blister fluid was approximately 26% lower than the AUC_{0-12h} in the serum of 10 healthy subjects.

In a single-dose study, tigecycline 100 mg was administered to subjects prior to undergoing elective surgery or medical procedure for tissue extraction. Concentrations at 4 hours after tigecycline administration were higher in gallbladder (38-fold, n=6), lung (3.7-fold, n=5), and colon (2.3-fold, n=6), and lower in synovial fluid (0.58-fold, n=5), and bone (0.35-fold, n=6) relative to serum. The concentration of tigecycline in these tissues after multiple doses has not been studied.

Elimination

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. Approximately 22% of the total dose is excreted as unchanged tigecycline in urine. Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline and its metabolites. Glucuronidation and renal excretion of unchanged tigecycline are secondary routes.

Specific Populations

Hepatic Impairment

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 (Child Pugh C) 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). Systemic clearance of tigecycline was reduced by 55%, and the half-life of tigecycline was prolonged by 43% in patients with severe hepatic impairment (Child Pugh C). Dosage adjustment is necessary in patients with severe hepatic impairment (Child Pugh C) *[see Use in Specific Populations (8.6) and Dosage and Administration (2.2)]*.

Renal Impairment

A single dose study compared 6 subjects with severe renal impairment (creatinine clearance < 30 mL/min), 4 end stage renal disease (ESRD) patients receiving tigecycline 2 hours before hemodialysis, 4 ESRD patients receiving tigecycline 1 hour after hemodialysis, and 6 healthy control subjects. The pharmacokinetic profile of tigecycline was not significantly 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.

Geriatric Patients

No significant differences in pharmacokinetics were observed between healthy elderly subjects (n=15, age 65 to 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 Use in Specific Populations (8.5)]*.

Pediatric Patients

A single-dose safety, tolerability, and pharmacokinetic study of tigecycline in pediatric patients aged 8 to 16 years who recently recovered from infections was conducted. The doses administered were 0.5, 1, or 2 mg/kg. The study showed that for children aged 12 to 16 years (n = 16) a dosage of 50 mg twice daily would likely result in exposures comparable to those observed in adults with the approved dosing regimen. Large variability observed in children aged 8 to 11 years of age (n = 8) required additional study to determine the appropriate dosage.

A subsequent tigecycline dose-finding study was conducted in 8 to 11 year old patients with cIAI, cSSSI, or CABP. The doses of tigecycline studied were 0.75 mg/kg (n = 17), 1 mg/kg (n = 21), and 1.25 mg/kg (n=20). This study showed that for children aged 8 to 11 years, a 1.2 mg/kg dose would likely result in exposures comparable to those observed in adults resulting with the approved dosing regimen *[see Dosage and Administration (2.3)]*.

Gender

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

Race

In a pooled analysis of 73 Asian subjects, 53 Black subjects, 15 Hispanic subjects, 190 White subjects, and 3 subjects classified as "other" participating in clinical pharmacology studies, there was no significant difference in the mean (± SD) tigecycline clearance among the Asian subjects (28.8 ± 8.8 L/h), Black subjects (23 ± 7.8 L/h), Hispanic subjects (24.3 ± 6.5 L/h), White subjects (22.1 ± 8.9 L/h), and "other" subjects (25 ± 4.8 L/h). Therefore, no dosage adjustment is necessary based on race.

Drug Interaction Studies

Digoxin

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

Warfarin

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%, an increase in C_{max} by 38% and 43% 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.

In vitro studies in human liver microsomes indicate that tigecycline does not inhibit metabolism mediated by any of the following 6 cytochrome P450 (CYP) isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. Therefore, tigecycline is not expected to alter the metabolism of drugs metabolized by these enzymes. In addition, because tigecycline is not extensively metabolized, clearance of tigecycline is not expected to be affected by drugs that inhibit or induce the activity of these CYP450 isoforms.

12.4 Microbiology

Mechanism of Action

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

Resistance

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

Interaction with Other Antimicrobials

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

Antimicrobial Activity

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

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

Gram-negative Bacteria
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Legionella pneumophila

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

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

Gram-positive Bacteria
Enterococcus avium
Enterococcus casseliflavus
Enterococcus faecalis (vancomycin-resistant isolates)
Enterococcus faecium (vancomycin-susceptible and -resistant isolates)
Enterococcus gallinarum
Listeria monocytogenes
Staphylococcus epidermidis (methicillin-susceptible and -resistant isolates)
Staphylococcus haemolyticus

Gram-negative Bacteria
*Acinetobacter baumannii**
Aeromonas hydrophila
Citrobacter koseri
Enterobacter aerogenes
Haemophilus influenzae (ampicillin-resistant)
Haemophilus parainfluenzae
Pasteurella multocida
Serratia marcescens
Stenotrophomonas maltophilia

Anaerobic Bacteria
Bacteroides distasonis
Bacteroides ovatus
Peptostreptococcus spp.
Porphyromonas spp.
Prevotella spp.

Other Bacteria
Mycobacterium abscessus
Mycobacterium fortuitum

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

Susceptibility Test Methods

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

Dilution Techniques:

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

Diffusion Techniques:

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

Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to tigecycline can be determined by a standardized test method [3,4]. The MIC values should be interpreted according to the criteria provided in Table 4.

Table 4. Susceptibility Test Result Interpretive Criteria for Tigecycline

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	S	I	R	S	I	R
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 0.5[a]	-	-	≥ 19	-	-
Streptococcus spp. other than *S. pneumoniae*	≤ 0.25[a]	-	-	≥ 19	-	-
Streptococcus pneumoniae	≤ 0.06[a]	-	-	≥ 19	-	-
Enterococcus faecalis (vancomycin-susceptible isolates)	≤ 0.25[a]	-	-	≥ 19	-	-
Enterobacteriaceae[b]	≤ 2	4	≥ 8	≥ 19	15 to 18	≤ 14
Haemophilus influenzae	≤ 0.25[a]	-	-	≥ 19	-	-
Anaerobes[c]	≤ 4	8	≥ 16	n/a	n/a	n/a

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

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

Quality Control:

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

Table 5. Acceptable Quality Control Ranges for Tigecycline

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of tigecycline. No mutagenic or clastogenic potential was found in a battery of tests, including *in vitro* chromosome aberration assay in Chinese hamster ovary (CHO) cells, *in vitro* forward mutation assay in CHO cells (HGRPT locus), *in vitro* forward mutation assays in mouse lymphoma cells, and *in vivo* mouse micronucleus assay. Tigecycline did not affect mating or fertility in rats at exposures up to 5 times the human daily dose based on AUC (28 mcg•hr/mL at 12 mg/kg/day). In female rats, there were no compound-related effects on ovaries or estrous cycles at exposures up to 5 times the human daily dose based on AUC.

13.2 Animal Toxicology and/or Pharmacology

In two week studies, decreased erythrocytes, reticulocytes, leukocytes, and platelets, in association with bone marrow hypocellularity, have been seen with tigecycline at exposures of 8 times and 10 times the human daily dose based on AUC in rats and dogs, (AUC of approximately 50 and 60 mcg•hr/mL at doses of 30 and 12 mg/kg/day) respectively. These alterations were shown to be reversible after two weeks of dosing.

14 CLINICAL STUDIES

14.1 Complicated Skin and Skin Structure Infections

Tigecycline was evaluated in adults for the treatment of complicated skin and skin structure infections (cSSSI) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 300 and 305). These studies compared tigecycline (100 mg intravenous initial dose followed by 50 mg every 12 hours) with vancomycin (1 g intravenous every 12 hours)/aztreonam (2 g intravenous every 12 hours) for 5 to 14 days. Patients with complicated deep soft tissue infections including wound infections and cellulitis (≥ 10 cm, requiring surgery/drainage or with complicated underlying disease), major abscesses, infected ulcers, and burns were enrolled in the studies. The primary efficacy endpoint was the clinical response at the test of cure (TOC) visit in the co-primary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) patients. See Table 6. Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 7.

Table 6. Clinical Cure Rates from Two Studies in Complicated Skin and Skin Structure Infections after 5 to 14 Days of Therapy

	Tigecycline[a] n/N (%)	Vancomycin/Aztreonam[b] n/N (%)
Study 300		
CE	165/199 (82.9)	163/198 (82.3)
c-mITT	209/277 (75.5)	200/260 (76.9)
Study 305		
CE	200/223 (89.7)	201/213 (94.4)
c-mITT	220/261 (84.3)	225/259 (86.9)

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

Table 7. Clinical Cure Rates by Infecting Pathogen in Microbiologically Evaluable Patients with Complicated Skin and Skin Structure Infections[a]

Pathogen	Tigecycline n/N (%)	Vancomycin/Aztreonam n/N (%)
Escherichia coli	29/36 (80.6)	26/30 (86.7)
Enterobacter cloacae	10/12 (83.3)	15/15 (100)
Enterococcus faecalis (vancomycin-susceptible only)	15/21 (71.4)	19/24 (79.2)
Klebsiella pneumoniae	12/14 (85.7)	15/16 (93.8)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	124/137 (90.5)	113/120 (94.2)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	79/95 (83.2)	46/57 (80.7)
Streptococcus agalactiae	8/8 (100)	11/14 (78.6)
Streptococcus anginosus grp[b]	17/21 (81.0)	9/10 (90.0)
Streptococcus pyogenes	31/32 (96.9)	24/27 (88.9)
Bacteroides fragilis	7/9 (77.8)	4/5 (80.0)

[a] Two cSSSI pivotal studies and two Resistant Pathogen studies
[b] Includes *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*

14.2 Complicated Intra-abdominal Infections

Tigecycline was evaluated in adults for the treatment of complicated intra-abdominal infections (cIAI) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 301 and 306). These studies compared tigecycline (100 mg intravenous initial dose followed by 50 mg every 12 hours) with imipenem/cilastatin (500 mg intravenous every 6 hours) for 5 to 14 days. Patients with complicated diagnoses including appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis were enrolled in the studies. The primary efficacy endpoint was the clinical response at the TOC visit for the co-primary populations of the 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 Rates from Two Studies in Complicated Intra-abdominal Infections after 5 to 14 Days of Therapy

	Tigecycline[a] n/N (%)	Imipenem/Cilastatin[b] n/N (%)
Study 301		
ME	199/247 (80.6)	210/255 (82.4)
m-mITT	227/309 (73.5)	244/312 (78.2)
Study 306		
ME	242/265 (91.3)	232/258 (89.9)
m-mITT	279/322 (86.6)	270/319 (84.6)

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

Table 9. Clinical Cure Rates by Infecting Pathogen in Microbiologically Evaluable Patients with Complicated Intra-abdominal Infections[a]

Pathogen	Tigecycline n/N (%)	Imipenem/Cilastatin n/N (%)
Citrobacter freundii	12/16 (75.0)	3/4 (75.0)
Enterobacter cloacae	15/17 (88.2)	16/17 (94.1)
Escherichia coli	284/336 (84.5)	297/342 (86.8)
Klebsiella oxytoca	19/20 (95.0)	17/19 (89.5)
Klebsiella pneumoniae	42/47 (89.4)	46/53 (86.8)
Enterococcus faecalis	29/38 (76.3)	35/47 (74.5)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	26/28 (92.9)	22/24 (91.7)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	16/18 (88.9)	1/3 (33.3)
Streptococcus anginosus grp[b]	101/119 (84.9)	60/79 (75.9)
Bacteroides fragilis	68/88 (77.3)	59/73 (80.8)
Bacteroides thetaiotaomicron	36/41 (87.8)	31/36 (86.1)
Bacteroides uniformis	12/17 (70.6)	14/16 (87.5)
Bacteroides vulgatus	14/16 (87.5)	4/6 (66.7)
Clostridium perfringens	18/19 (94.7)	20/22 (90.9)
Peptostreptococcus micros	13/17 (76.5)	8/11 (72.7)

[a] Two cIAI pivotal studies and two Resistant Pathogen studies
[b] Includes *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*

14.3 Community-Acquired Bacterial Pneumonia

Tigecycline was evaluated in adults for the treatment of community-acquired bacterial pneumonia (CABP) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 308 and 313). These studies compared tigecycline (100 mg intravenous initial dose followed by 50 mg every 12 hours) with levofloxacin (500 mg intravenous every 12 or 24 hours). In one study (Study 308), after at least 3 days of intravenous therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms. Total therapy was 7 to 14 days. Patients with community-acquired bacterial pneumonia who required hospitalization and intravenous therapy were enrolled in the studies. The primary efficacy endpoint was the clinical response at the test of cure (TOC) visit in the co-primary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) patients. See Table 10. Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 11.

Table 10. Clinical Cure Rates from Two Studies in Community-Acquired Bacterial Pneumonia after 7 to 14 Days of Total Therapy

	Tigecycline[a] n/N (%)	Levofloxacin[b] n/N (%)	95% CI[c]
Study 308[d]			
CE	125/138 (90.6)	136/156 (87.2)	(-4.4, 11.2)
c-mITT	149/191 (78)	158/203 (77.8)	(-8.5, 8.9)
Study 313			
CE	128/144 (88.9)	116/136 (85.3)	(-5, 12.2)
c-mITT	170/203 (83.7)	163/200 (81.5)	(-5.6, 10.1)

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] Levofloxacin (500 mg intravenous every 12 or 24 hours)
[c] 95% confidence interval for the treatment difference
[d] After at least 3 days of intravenous therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms in Study 308.

Table 11. Clinical Cure Rates by Infecting Pathogen in Microbiologically Evaluable Patients with Community-Acquired Bacterial Pneumonia[a]

Pathogen	Tigecycline n/N (%)	Levofloxacin n/N (%)
Haemophilus influenzae	14/17 (82.4)	13/16 (81.3)
Legionella pneumophila	10/10 (100.0)	6/6 (100.0)
Streptococcus pneumoniae (penicillin-susceptible only)[b]	44/46 (95.7)	39/44 (88.6)

[a] Two CABP studies
[b] Includes cases of concurrent bacteremia [cure rates of 20/22 (90.9%) versus 13/18 (72.2%) for tigecycline and levofloxacin respectively]

To further evaluate the treatment effect of tigecycline, a post-hoc analysis was conducted in CABP patients with a higher risk of mortality, for whom the treatment effect of antibiotics is supported by historical evidence. The higher-risk group included CABP patients from the two studies with any of the following factors:

- Age ≥ 50 years
- PSI score ≥ 3
- *Streptococcus pneumoniae* bacteremia

The results of this analysis are shown in Table 12. Age ≥ 50 was the most common risk factor in the higher-risk group.

Table 12. Post-hoc Analysis of Clinical Cure Rates in Patients with Community-Acquired Bacterial Pneumonia Based on Risk of Mortality[a]

	Tigecycline n/N (%)	Levofloxacin n/N (%)	95% CI[b]
Study 308[c]			
CE			
Higher risk			
Yes	93/103 (90.3)	84/102 (82.4)	(-2.3, 18.2)
No	32/35 (91.4)	52/54 (96.3)	(-20.8, 7.1)
c-mITT			
Higher risk			
Yes	111/142 (78.2)	100/134 (74.6)	(-6.9, 14)
No	38/49 (77.6)	58/69 (84.1)	(-22.8, 8.7)
Study 313			
CE			
Higher risk			
Yes	95/107 (88.8)	68/85 (80)	(-2.2, 20.3)
No	33/37 (89.2)	48/51 (94.1)	(-21.1, 8.6)
c-mITT			
Higher risk			
Yes	112/134 (83.6)	93/120 (77.5)	(-4.2, 16.4)
No	58/69 (84.1)	70/80 (87.5)	(-16.2, 8.8)

[a] Patients at higher risk of death include patients with any one of the following: ≥ 50 years of age; PSI score ≥ 3; or bacteremia due to *Streptococcus pneumoniae*
[b] 95% confidence interval for the treatment difference
[c] After at least 3 days of intravenous therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms in Study 308.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Tigecycline for injection, USP is supplied in a single dose 10 mL glass vial, containing 50 mg tigecycline lyophilized powder for reconstitution. The 10 mL vials are supplied in packages of ten (NDC # 63323-960-10).

Prior to reconstitution, Tigecycline for injection, USP should be stored at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

The reconstituted solution of Tigecycline for injection, USP 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 intravenous bag) *[see Dosage and Administration (2.1)]*.

The container closure is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

- Advise patients, their families, or caregivers that diarrhea is a common problem caused by antibacterial drugs. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, tell them to contact his or her healthcare provider *[see Warnings and Precautions (5.8)]*.
- Patients should be counseled that antibacterial drugs including tigecycline should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When tigecycline is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by tigecycline or other antibacterial drugs in the future.

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