PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# PrTIGECYCLINE FOR INJECTION

Tigecycline for Injection

Sterile, lyophilized powder, 50 mg/vial, for intravenous use
Manufacturer's Standard

Tetracycline Antibiotic
(glycylcycline derivative)

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Date of Initial Authorization:
MAY 4, 2022

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## RECENT MAJOR LABEL CHANGES

None at the time of Authorization

**TABLE OF CONTENTS**
**Sections or subsections that are not applicable at the time of authorization are not listed .**

## PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

TIGECYCLINE FOR INJECTION (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 (cSSSI) 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 (cIAI) 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 (CAP) (mild to moderate infections only) caused by *Haemophilus influenzae*, *Streptococcus pneumoniae* (penicillin-susceptible isolates only), *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.

TIGECYCLINE FOR INJECTION (tigecycline) is not indicated for the treatment of hospital-acquired or ventilator-associated pneumonia. See 7 WARNINGS AND PRECAUTIONS, General.

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 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. Once these results are available, antimicrobial therapy should be adjusted if necessary. TIGECYCLINE FOR INJECTION 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 FOR INJECTION.

### 1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. See 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics.

### 1.2 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness. A brief discussion can be found in 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics.

## 2 CONTRAINDICATIONS

TIGECYCLINE FOR INJECTION (tigecycline) is contraindicated in patients who are hypersensitive to tigecycline or tetracycline class of antibiotics or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

Based on pharmacokinetic data in patients with severe hepatic impairment (Child Pugh C), the dose of TIGECYCLINE FOR INJECTION (tigecycline) should be altered. See 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment.

### 4.2 Recommended Dose and Dosage Adjustment

Health Canada has not authorized an indication for pediatric use.

The recommended dosage regimen of TIGECYCLINE FOR INJECTION is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous (IV) 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 cSSSI or for cIAI is 5 to 14 days.

The recommended duration of treatment with TIGECYCLINE FOR INJECTION for CAP (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 FOR INJECTION is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). See 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, 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 FOR INJECTION 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 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency.

Patients with Renal Insufficiency

Based on the pharmacokinetic data, no dosage adjustment of TIGECYCLINE FOR INJECTION is necessary in patients with renal impairment or in patients undergoing hemodialysis. See 10 CLINICAL

PHARMACOLOGY, 10.3, Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency.

Other

No dosage adjustment of TIGECYCLINE FOR INJECTION is necessary based on age (adults 18 years of age or more), gender or race. See 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions.

### 4.3 Reconstitution

**Parenteral Products**:

**Table 1 - Reconstitution**

| Vial Size | Volume of Diluent to be Added to Vial | Approximate Available Volume | 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 FOR INJECTION 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 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 IV bag). 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 IV bag. See 11 STORAGE, STABILITY AND DISPOSAL.

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).

### 4.4 Administration

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

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 either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. Injection should be made with an infusion solution compatible with TIGECYCLINE FOR INJECTION and with any other drug(s) administered via this common line.

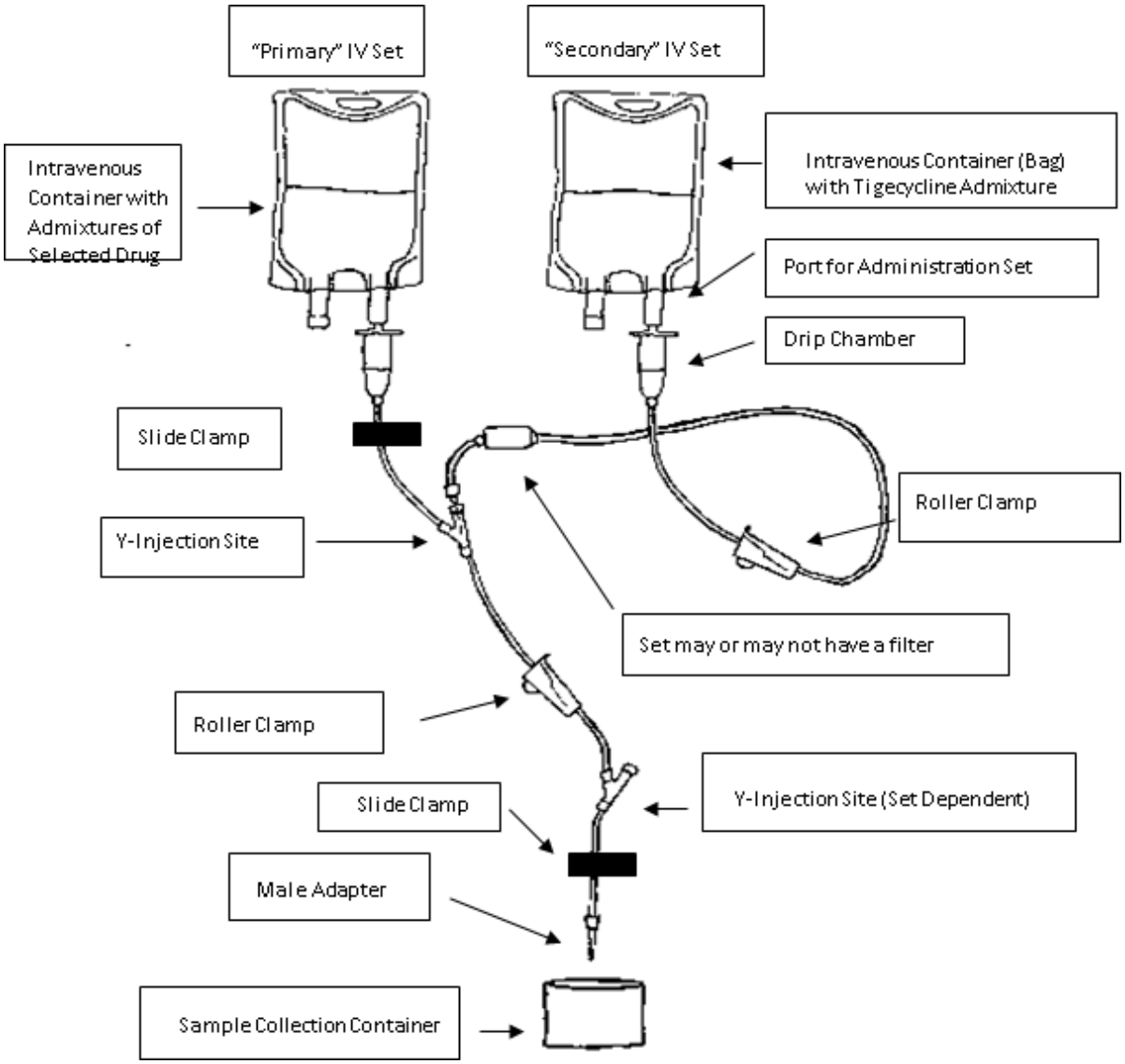
When administered through a Y-site, TIGECYCLINE FOR INJECTION, is compatible with the following drugs or diluents when used with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection USP:

- 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 mcg/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 FOR INJECTION: 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**



### 4.5 Missed Dose

This information is not available for this drug product.

## 5 OVERDOSAGE

No specific information is available on the treatment of overdose with TIGECYCLINE FOR INJECTION (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 management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 2 – Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Intravenous infusion | Sterile, lyophilized powder<br>50 mg tigecycline per vial | L-arginine, hydrochloric acid<br>and sodium hydroxide |

TIGECYCLINE FOR INJECTION (tigecycline) for injection is supplied in a single-dose 5 mL Type I glass vial.

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

Supplied 10 vials/box.

## 7 WARNINGS AND PRECAUTIONS

**<u>All-Cause Mortality</u>**

**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% (150/3788) 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. An analysis of mortality in all trials conducted for approved indications (cSSSI, cIAI, and CAP), including post-market trials showed an adjusted mortality rate of 2.5% (66/2640) for tigecycline and 1.8% (48/2628) 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 FOR INJECTION should be reserved for use in situations when alternative treatments are not suitable**. See 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions, Adverse events with outcome of Death.

**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 8 ADVERSE REACTIONS, 8.5 Post-Market 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.

The use of tigecycline with other drugs may lead to drug-drug interactions and require dose adjustment and monitoring. See 9 DRUG INTERACTIONS; see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.

TIGECYCLINE FOR INJECTION 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.

Caution should be exercised when considering TIGECYCLINE FOR INJECTION monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. See 8 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.

TIGECYCLINE FOR INJECTION 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 14 CLINICAL TRIALS. TIGECYCLINE FOR INJECTION has not been evaluated in clinical trials for use against suspected or documented multiple drug resistant pathogens in pneumonia.

**Mortality imbalance and lower cure rates in hospital-acquired pneumonia**

TIGECYCLINE FOR INJECTION is **not** indicated for treatment of hospital acquired pneumonia (HAP). The safety and efficacy of tigecycline in patients with HAP have not been established. In a study of hospital acquired pneumonia patients, the sub-group of patients with ventilator-associated pneumonia (VAP) who received tigecycline had lower cure rates (47.9% versus 70.1% for the clinically evaluable population) and greater mortality (25/131 [19.1%] versus 15/122 [12.3%]) than the comparator. Of those patients with VAP and bacteremia at baseline, those who received tigecycline had greater mortality (9/18 [50.0%] versus 1/13 [7.7%]) than the comparator.

**Cardiovascular**

An effect on cardiac repolarization following tigecycline administration cannot be definitively excluded from the clinical data. See 10 CLINICAL PHARMACOLOGY,10.3 Pharmacokinetics, 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 pro-arrhythmic 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 FOR INJECTION should not be exceeded. See 4 DOSAGE AND ADMINISTRATION.

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

**Driving and Operating Machinery**

Tigecycline can cause dizziness. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

**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 8 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.

**Monitoring and Laboratory Tests**

Monitoring of blood coagulation parameters, including blood fibrinogen, is recommended prior to treatment initiation with tigecycline and regularly while on treatment.

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

Monitoring of calcineurin inhibitor (tacrolimus, cyclosporine) blood levels before, during and following treatment with tigecycline, together with appropriate dose adjustment, is recommended. See 9 DRUG INTERACTIONS, 9.2 Drug Interactions Overview.

**Reproductive Health: Female and Male Potential**

- **Fertility**

The effects of tigecycline on fertility in humans have not been studied. Nonclinical studies conducted with tigecycline in rats do not indicate harmful effects with respect to fertility or reproductive performance.

**Sensitivity/Resistance**

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 risks the development of drug-resistant bacteria.

### 7.1 Special Populations

#### 7.1.1 Pregnant Women

There are no adequate and well-controlled studies of tigecycline in pregnant women. TIGECYCLINE FOR INJECTION 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) have been observed with tigecycline. See 16 NON-CLINICAL TOXICOLOGY.

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

### 7.1.2 Breast-feeding

It is not known whether this drug is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of tigecycline/metabolites in milk. See *16* NON-CLINICAL TOXICOLOGY*, Reproductive and Developmental Toxicology.* 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 FOR INJECTION should not be administered to a nursing woman unless the potential benefit to the mother outweighs any possible risk to the child. See 7 WARNINGS AND PRECAUTIONS, General.

### 7.1.3 Pediatrics

**Pediatrics (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. Pediatric clinical trials to evaluate the safety and efficacy of tigecycline were not conducted because of the higher risk of mortality seen in adult trials. Tigecycline can cause teeth discoloration in children less than 8 years of age. See 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Pediatrics.

### 7.1.4 Geriatrics

**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.

## 8 ADVERSE REACTIONS

### 8.1 Adverse 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 averageover 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%).

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 14 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 3 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 3: 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.

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-treated and comparator-treated patients. Risk differences in the treatments by infection type are provided in Table 4. 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 4: 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).

An analysis of mortality in all trials conducted for approved indications (cSSSI, cIAI, and CAP), including post-market trials (315, 400, 900) showed an adjusted mortality rate of 2.5% (66/2640) for tigecycline and 1.8% (48/2628) for comparator, respectively. The adjusted risk difference for mortality stratified by trial weight was 0.6% (95% CI 0.0, 1.2).

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 7 WARNINGS AND PRECAUTIONS, General. 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.

### 8.2.1 Clinical Trial Adverse Reactions – Pediatrics

This information is not available for this drug product.

### 8.3 Less Common Clinical Trial Adverse Reactions

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.

#### 8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

This information is not available for this drug product.

### 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

See Table 3.

### 8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post approval use of tigecycline:

Acute pancreatitis including fatal cases, anaphylaxis/anaphylactoid reactions, severe skin reactions including Stevens-Johnson Syndrome, thrombocytopenia, hepatic cholestasis and hypofibrinogenemia (including bleeding events, some serious).

There has been one case of ventricular arrhythmia (with positive dechallenge and rechallenge) associated with tigecycline administration.

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

Tacrolimus, cyclosporine (calcineurin inhibitors): Clinically significant increases in blood trough concentrations of tacrolimus and cyclosporine requiring dose adjustment, have been reported with concomitant use of tigecycline. See 9, DRUG INTERACTIONS, 9.4 Drug-Drug Interactions.

*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.

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

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

### 9.3 Drug-Behavioural Interactions

This information is not available for this drug product.

### 9.4 Drug-Drug Interactions

**Table 5 - Established or Potential Drug-Drug Interactions**

| [Proper / Common name] | Source of Evidence | Effect | Clinical comment |
|---|---|---|---|
| tacrolimus | C | Increased tacrolimus trough blood levels 3.2 to 3.8-fold within 1 to 10 days of tigecycline initiation. | Tacrolimus dose adjustment during and following tigecycline therapy, based on therapeutic concentration monitoring, is recommended. Two case reports described implementing a reduction in the tacrolimus daily dose from 7 mg to 2 mg during tigecycline therapy, and a dose increase upon cessation of tigecycline therapy. In one of the two cases, the tacrolimus dose reduction followed withholding tacrolimus for 2 days. |
| cyclosporine | C | Increased cyclosporine trough blood levels 1.4- fold within 4 days of tigecycline initiation. | Cyclosporine dose adjustment, during and following tigecycline therapy, based on therapeutic concentration monitoring, is recommended. One case report described with holding cyclosporine for one day, followed by a reduction in the cyclosporine daily dose from 120 mg to 60 mg, during tigecycline therapy, and a dose increase upon cessation of tigecycline therapy. |

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

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 pharmacodynamic effects of digoxin as measured by changes in ECG intervals. In addition, digoxin did not affect the pharmacokinetic profile of tigecycline. Therefore, no dosage adjustment is necessary when tigecycline is administered with digoxin.

Concomitant administration of tigecycline (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single-dose) to healthy subjects resulted in a decrease in clearance of R-warfarin and S-warfarin by 40% and 23%, and an increase in AUC by 68% and 29%, respectively. Tigecycline did not significantly alter the effects of warfarin on 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.

### 9.5 Drug-Food Interactions

Interactions with food have not been established.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

### 10.1 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 15 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.)

### 10.2 Pharmacodynamics

This information is not available for this drug product.

### 10.3 Pharmacokinetics

The mean pharmacokinetic parameters of tigecycline after single and multiple intravenous doses are summarized in Table 6. Intravenous infusions of tigecycline were administered over approximately 30 to 60 minutes.

**Table 6: Mean (CV%) Pharmacokinetic Parameters of Tigecycline**

| | Single Doses 100 mg | Multiple Doses[a] 50 mg q12h |
|---|---|---|
| $C_{max}$ (mcg/mL)[b] | 1.45 (22%) | 0.87 (27%) |
| $C_{max}$ (mcg/mL)[c] | 0.90 (30%) | 0.63 (15%) |
| AUC (mcg·hr/mL) | 5.19 (36%) | - - |
| $AUC_{0-24h}$ (mcg·hr/mL) | - - | 4.70 (36%) |
| $C_{min}$ (mcg/mL) | - - | 0.13 (59%) |
| $t_{½}$ (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 mcg/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 $AUC_{0\text{-}12h}$ (134 mcg·hr/mL) in alveolar cells was approximately 77.5-fold higher than the $AUC_{0\text{-}12h}$ in the serum of these subjects, and the $AUC_{0\text{-}12h}$ (2.28 mcg·hr/mL) in epithelial lining fluid was approximately 32% higher than the $AUC_{0\text{-}12h}$ in serum. In a skin blister study, the $AUC_{0\text{-}12h}$ (1.61 mcg·hr/mL) of tigecycline in skin blister fluid was approximately 26% lower than the $AUC_{0\text{-}12h}$ 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.

**Elimination:**

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

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

**Special Populations and Conditions:**

- **Pediatrics:** Tigecycline pharmacokinetics was investigated in two studies. No loading dose was administered in these studies. In a single dose study in children aged 8-16 years (n=24) tigecycline (0.5, 1, or 2 mg/kg to a maximum dose of 50, 100, or 150 mg, respectively) was administered intravenously over 30 minutes under fed conditions. Two out of six children aged 8-11 years receiving a dose of 1 mg/kg vomited therefore the 2 mg/kg dose was not evaluated in this age group. The study showed that for children aged 12-16 years (n=16) a dose of 50 mg every 12 hours would likely result in drug exposures comparable to those observed in adults. Large variability was observed in children aged 8 to 11 years of age (n = 8).

  In a subsequent dose-finding study, children aged 8 to 11 years of age with cIAI, cSSSI, or CAP received multiple doses of tigecycline (0.75 mg/kg, 1 mg/kg, or 1.25 mg/kg up to a maximum dose of 50 mg) every 12 hours intravenously over 30 minutes. Simulations of the $AUC_{0\text{-}24h}$ using clearance values from participating children indicated a 1.2 mg/kg dose (to a maximum of 50 mg) every 12 hours would likely result in exposures comparable to those observed in adults with the approved dosing regimen. Higher incidence of treatment-emergent adverse reactions, i.e., nausea 48.3% and vomiting 46.6% were reported in children as compared with adverse reactions reported from clinical studies in adults, i.e, (nausea 21% and vomiting 13%).

- **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 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics.

- **Sex:** 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 sex.

- **Ethnic Origin:** 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 ethnic origin.

- **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 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment.

- **Renal Insufficiency:** A single dose study compared 6 subjects with severe renal impairment (creatinine clearance ≤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 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment.

- **Cardiovascular:** 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 ≥ 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 ≤10 msec, without associated drug-related adverse cardiac events being reported in concert with any significant changes in QTc.

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.

## 11 STORAGE, STABILITY AND DISPOSAL

Prior to reconstitution, TIGECYCLINE FOR INJECTION (tigecycline) lyophilized powder should be stored at a controlled room temperature 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F) for up to the expiration date specified on the label. 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 IV bag). Alternatively, TIGECYCLINE FOR INJECTION mixed with 0.9% Sodium Chloride Injection, USP, 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 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-red 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. Any unused medicinal product should be disposed of in accordance with local requirements.

## 12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for this product.

## PART II: SCIENTIFIC INFORMATION

## 13 PHARMACEUTICAL INFORMATION

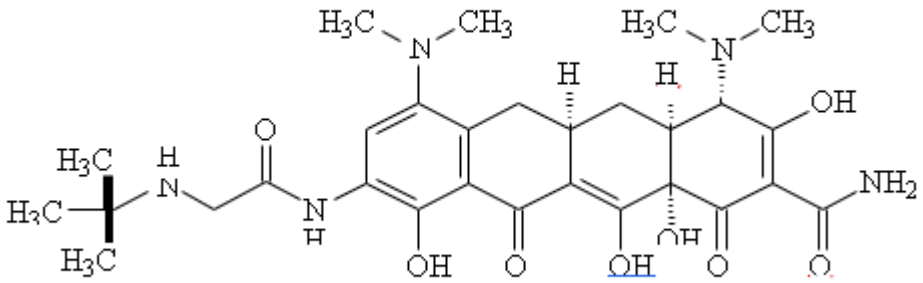
### Drug Substance

Proper 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-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

Molecular formula and molecular mass: $C_{29}H_{39}N_5O_8$ (585.65 g/mol)

Structural formula:



Physicochemical properties: Tigecycline is an orange powder. The reconstituted solution is orange to red 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 175°C - 180°C.

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

## 14 CLINICAL TRIALS

### 14.1 Trial Design and Study Demographics

**Complicated Skin and Skin Structure Infections (cSSSI)**

Tigecycline was studied for the treatment of 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 7: Phase 3 Clinical Studies for cSSSI – Study Demographics and Trial Design**

| Study No. | Study Design | No. 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)<br><br>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)<br><br>Vancomycin + aztreonam Arm: 1 g vancomycin+ 2 g aztreonam every 12 hours (5–14 days) |

**Complicated Intra-abdominal Infections (cIAI)**

TIGECYCLINE FOR INJECTION was studied for the treatment of 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 8: Phase 3 Clinical Studies for cIAI – Study Demographics and Trial Design**

| Study No. | Study Design | No. 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<br>18–91 years<br>(43.6 years) | Tigecycline Arm:<br>100 mg loading, 50 mg maintenance every 12 hours over 30 minutes<br>(5-14 days)<br><br>Imipenem/Cilastatin Arm:<br>500 mg every 6 hours<br>(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<br>18–88 years<br>(48.9 years) | Tigecycline Arm:<br>100 mg loading, 50 mg maintenance every 12 hours over 30 minutes<br>(5-14 days)<br><br>Imipenem/Cilastatin Arm:<br>500 mg every 6 hours<br>(5-14 days) |

**Community Acquired Pneumonia (CAP) (mild to moderate infections only)**

TIGECYCLINE FOR INJECTION was studied for the treatment of CAP (mild to moderate infections only) in 2 clinical trials.

Patients (18 years of age or older) with CAP 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 CAP 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 9: Phase 3 Clinical Studies for CAP – Study Demographics and Trial Design**

| Study No. | Study Design | No. 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<br>18-91years<br>(55 years) | Tigecycline Arm:<br>100 mg loading, 50 mg maintenance every 12 hours over 30 minutes<br>(7-14 days) |

**Table 9: Phase 3 Clinical Studies for CAP – Study Demographics and Trial Design**

| Study No. | Study Design | No. Subjects Randomized | Demography: Sex, Age Range (Mean Age), | IV Dose and Frequency (Duration of Treatment) |
|---|---|---|---|---|
| | | | | Levofloxacin Arm:<br>500 mg levofloxacin every 24 hours (7-14 days)<br><br>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<br>17-92 years<br>(50 years) | Tigecycline Arm:<br>100 mg loading, 50 mg maintenance every 12 hours over 60 minutes (7–14 days)<br><br>Levofloxacin Arm:<br>500 mg levofloxacin IV every 12 or 24 hours<br><br>(7-14 days) |

### 14.2 Study Results

**Complicated Skin and Skin Structure Infections (cSSSI)**

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 10. Clinical cure rates at TOC by pathogen in the microbiologically evaluable (ME) patients are presented in Table 11.

**Table 10: Clinical Cure[b] Rates in cSSSI**

| | 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 11: Clinical Cure Rates By Infecting Pathogen in ME Patients with cSSSI [a]**

| Pathogen | Tigecycline n / N (%) | Comparator n / N (%) |
|---|---|---|
| *Escherichia coli* | 25/29 (86.2) | 26/30 (86.7) |

**Table 11: Clinical Cure Rates By Infecting Pathogen in ME Patients with cSSSI [a]**

| Pathogen | Tigecycline n / N (%) | Comparator n / N (%) |
|---|---|---|
| *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 (cIAI)**

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 ME and the microbiologic modified intent to treat (m-mITT) patients. See Table 12. Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 13.

**Table 12: Clinical Cure[b] Rates in cIAI**

| | 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 13: Clinical Cure Rates By Infecting Pathogen in ME Patients with cIAI [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) |

**Table 13: Clinical Cure Rates By Infecting Pathogen in ME Patients with cIAI[a]**

| Pathogen | Tigecycline n / N (%) | Comparator n / N (%) |
|---|---|---|
| *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 (CAP) (mild to moderate infections only)**

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 CE and c-mITT patients. See Table 14. Clinical cure rates at TOC by pathogen in the ME patients are presented in Table15.

**Table 14: Clinical Cure[b] Rates in CAP**

| | 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 Intervals (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 FOR INJECTION is not indicated for severe CAP.

**Table 15: Clinical Cure Rates By Infecting Pathogen in ME Patients with CAP[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) |

**Table 15: Clinical Cure Rates By Infecting Pathogen in ME Patients with CAP[a]**

| Pathogen | Tigecycline n/N (%) | Comparator n/N (%) |
|---|---|---|
| *Chlamydia pneumoniae* | 18/19 (94.7) | 26/27 (96.3) |

[a] · Two CAP pivotal studies

## 15 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.

**Susceptibility Test Methods**

*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 using testing medium that is fresh (<12 hours 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 mcg 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 mcg 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**

| Pathogen | Minimum Inhibitory Concentrations (mcg/mL) | | | Disk Diffusion (zone diameters in mm) | | |
|---|---|---|---|---|---|---|
| | 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 |

S= Susceptible; I=Intermediate; R=Resistant

[a.] The current absence of resistant isolates precludes defining any results other than "susceptible." Isolates yielding MIC results suggestive of "non-susceptible" category should be submitted to 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 mcg 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 (mcg/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 |

**Table 17: Acceptable Quality Control Ranges for Susceptibility Testing**

| QC organism | Minimum Inhibitory Concentrations (mcg/mL) | Disk Diffusion (zone diameters in mm) |
|---|---|---|
| *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 (mcg/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 |

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

| Organism | Number of Isolates | Range | MIC (mcg/mL) 50% | 90% |
|---|---|---|---|---|
| *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 | Range | MIC (mcg/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- | 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 |

**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 | Range | MIC (mcg/mL) 50% | 90% |
|---|---|---|---|---|
| *Salmonella enterica* ser. Paratyphi | 261 | 0.12-2 | 0.5 | 0.5 |
| *Salmonella enterica* ser. | 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 |
| *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.* [a] | 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

## 16 NON-CLINICAL TOXICOLOGY

**General 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.

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 ≥ 20 mg/kg/day in rats and ≥ 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 (≥ 10 mcg/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.

**Reproductive and Developmental Toxicology:**

*Reproduction Toxicity:* 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).

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.

*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 mcg •h/mL, which is equivalent to an $AUC_{0-24}$ of 6.1 mcg •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.<br>• Animals were observed for up to 15 days after dosing.<br>• All animals died at 175 mg/kg.<br>• One female died at 87.5 mg/kg.<br>• Decreased motor activity, ptosis, dyspnea, exophthalmia, lacrimation, and red pigmentation around eye(s) at 87.5 mg/kg.<br>• ~ 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.<br>• Animals were observed for up to 15 days after dosing.<br>• All animals died at ≥ 150 mg/kg. No mortality at 75 mg/kg.<br>• Immobility, decreased motor activity, ptosis, dyspnea, exophthalmia, erythema (ears, tail, and feet), low carriage, and edema (feet and head).<br>• ~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.<br>• Mean day 15 values for dosages 42.3 and 84.7 mg/kg/day were, respectively:<br>Cmax (mcg/mL): 19, 39<br>$AUC_{0-24}$ (mcg•h/mL): 35, 105. |

**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 |
|---|---|---|---|---|
| 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 post mortem examinations.<br>• No tigecycline-related mortality.<br>• Injection site lesions at 70 mg/kg/day required the euthanasia of 3 animals.<br>• Clinical signs (salivation, red pigmentation around the eyes, nose, and mouth, lacrimation, soft feces, and erythema) were observed at ≥ 30 mg/kg/day.<br>• 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.<br>• At 30 and 70 mg/kg/day, injection site lesions, including hemorrhage, inflammation, venous thrombosis, and venous necrosis occurred with increased incidence and frequency.<br>• Red pigmentation around the genitalia occurred in a few rats at 70 mg/kg/day.<br>• 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).<br>Food consumption was reduced at 70 mg/kg/day in males.<br>• 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.<br>• Yellow discoloration of the bone and decreased thymus size were seen at 70 mg/kg/day. |

**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 |
|---|---|---|---|---|
| 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.<br>• The NTEL was 5 mg/kg/day.<br>• Tigecycline $AUC_{0-24}$ may be underestimated by approximately 20% due to documented sample degradation.<br>• Mean day 14 values for dosages 5, 30, and 70 mg/kg/day, respectively were:<br>$C_{5min}$ (mcg/mL):<br>males: 7.46, 119, 152<br>females: na, 86.9, na<br>$AUC_{0-24}$ (mcg •h/mL):<br>males: 7.12, 65.9, 129<br>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 post mortem examinations.<br>• Mortality at 70 mg/kg/day was due to compound-related toxicity affecting various organ systems, primarily the hemopoietic system.<br>• 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-sustained convulsions, swollen muzzle, lying on side, slight dehydration, hunched posture, shallow breathing, |

**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 |
|---|---|---|---|---|
| Repeat-Dose RPT-42195 (cont'd) | | | | cold to touch, pale eyes, teeth grinding, weakness, loss of consciousness, and moderate to severe tremors at ≥ 50 mg/kg/day.<br>• Weight loss occurred at >50 mg/kg/day while decreased body weight gain was seen at >20 mg/kg/day.<br>• Decreased food consumption occurred at 70 mg/kg/day.<br>• 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.<br>• Decreased triglycerides occurred in males at > 20 mg/kg/day.<br>• Increased bilirubin occurred at >50 mg/kg/day. Decreased unsaturated iron binding capacity occurred in males at 70 mg/kg/day.<br>• 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.<br>• Tigecycline-related microscopic findings in other tissues at scheduled necropsy included minimal to marked bone marrow hypocellularity and decreased extramedullary 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 |

**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 |
|---|---|---|---|---|
| Repeat-Dose RPT-42195 (cont'd) | | | | 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.<br>• 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.<br>• Evidence of reversibility by the end of the 3-week recovery period was observed for most tigecycline-related antemortem and post mortem changes, except that red cell distribution width remained elevated, heart lesions (myocardial inflammation, atrial thrombosis in a single 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; | 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.<br>• Clinical signs (vocalization) were observed at 20 mg/kg/day.<br>• Decreased body-weight gain and body weights were observed at 20 mg/kg/day (body-weight loss did not occur). |

**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 |
|---|---|---|---|---|
| Repeat-Dose RPT-41074 (cont'd) | 177 – 214 g (males), 138 – 168 g (females) | | | • 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.<br>• 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.<br>• The NTEL was 2 mg/kg/day.<br>• Mean day 90 values for dosages 2, 6, and 20 mg/kg/day were, respectively:<br>$C_{5min}$ (mcg/mL):<br>males: 2.41, 12.7, 86.5<br>females: na, 11.2 , na<br>$AUC_{0-24}$ (mcg•h/mL):<br>males: 6.23, 19.9, 87.3<br>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 post mortem examinations.<br>• Mean day 15 values for dosages 2, 5, and 12 mg/kg/day were, respectively:<br>$C_{5min}$ (mcg/mL): 2.76, 11.12, 42.46<br>$AUC_{0-\infty}$ (mcg •h/mL): 6.08, 12.3, 34. |

**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 |
|---|---|---|---|---|
| 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 post mortem examinations.<br>• Four (4) of 6 dogs at 20 mg/kg/day were euthanized during week 2 due to severe physical debilitation.<br>• 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.<br>• Body-weight loss and decreased food consumption were observed at ≥ 12 mg/kg/day.<br>• Decreased platelets, reticulocytes, and WBCs occurred at > 5 mg/kg/day; these effects were toxicologically significant at ≥ 12 mg/kg/day.<br>• Thrombocytopenia occurred at 20 mg/kg/day.<br>• Increased APTT, increased cholesterol, and decreased glucose occurred at >12 mg/kg/day.<br>• Increased fibrinogen and inorganic phosphorous, decreased serum proteins (albumin and globulin) and thyroxine occurred at 20 mg/kg/day.<br>• Decreased weights of heart, kidney, testes, and increased adrenal weight occurred at 20 mg/kg/day.<br>• Lymphoid depletion/atrophy (lymph nodes, spleen, thymus) occurred at ≥ 12 mg/kg/day. |

**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 |
|---|---|---|---|---|
| Repeat-Dose Pivotal GTR-31609 (cont'd) | | | | • 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.<br>• 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.<br>• The NTEL was 5 mg/kg/day.<br>• Mean day 14 values for dosages 2, 5, 12 and 20 mg/kg/day, respectively were:<br>$C_{5min}$ (mcg /mL): 3.17, 14.9, 56.2, 91.4<br>$AUC_{0-24}$(mcg •h/mL): 5.48, 17.1, 59.9, 149. |
| Repeat-Dose Pivotal RPT-42488 | Dogs; Beagle; 6/sex/dosage, 3/sex/dosage retained for recovery; ~ 6 – 7 months; 9.0 – 12.1 kg (males), 5.8 – 9.8 kg (females) | IV, bolus (needle); once daily for 14 days, 3-week recovery | 0 (0 mg/mL), 5 (5 mg/mL), 12 (12 mg/mL); 1 mL/kg; pH of dosing solutions ranged from 7.79 to 7.88 | • Evaluations were based on mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry, urinalysis, histamine analysis, organ weights, and macroscopic and microscopic postmortem examinations.<br>• 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.<br>• Body-weight loss occurred at 12 mg/kg/day |

**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 |
|---|---|---|---|---|
| Repeat-Dose Pivotal RPT-42488 (cont'd) | | | | • Decreased food consumption was observed at ≥5 mg/kg/day.<br>• 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.<br>• Increased BUN, creatinine, and prolonged APTT (in males) occurred at 12 mg/kg/day.<br>• Increased incidence and/or severity of hematuria occurred at > 5 mg/kg/day at the end of the dosing period.<br>• Serum histamine levels were increased at ≥ 5 mg/kg/day on days 1 through 7 at both 5 minutes and 20 minutes after dosing.<br>• Microscopic findings consisted of lymphoid atrophy in the thymus and renal tubular degeneration at ≥ 5 and 12 mg/kg/day, respectively.<br>• Recovery of the antemortem findings was evident by the end of the 3-week compound-free period.<br>• 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. |

**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 |
|---|---|---|---|---|
| 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 postmortem examinations.<br>• 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.<br>• 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.<br>• Lymphoid atrophy of the thymus occurred at 5 mg/kg/day.<br>• The NOAEL/NTEL was 1.5 mg/kg/day.<br>• Mean day 75 values for dosages 0.5, 1.5, and 5 mg/kg/day were, respectively:<br>$C_{5min}$ (mcg /mL): 0.55, 1.85, 15.7<br>$AUC_{0-24}$ (mcg•h/mL): 1.61, 4.48, 19.3. |
| **Genotoxicity** | | | | |
| Forward Mutation Assay | CHO Cells | *In Vitro* | 25 to 2000 mcg/mL; NA | • Negative. |
| Forward Mutation Assay | Mouse Lymphoma Cells | *In Vitro* | 6.25 to 500 mcg/mL; NA | • Negative. |
| Forward Mutation Assay | Mouse Lymphoma Cells | *In Vitro* | 6.25 to 400 mcg/mL; NA | • Negative. |

**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 |
|---|---|---|---|---|
| Chromosome Aberration | CHO Cells | *In Vitro* | 0.291 to 1000 mcg/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, continuing throughout cohabitation, and through GD 16 | 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.<br>• 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 interrelated with reduced fetal weights and/or increased incidence of resorptions that occurred in these groups.<br>• 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.<br>• 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. |

**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 |
|---|---|---|---|---|
| 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.<br>• No effects on mating or fertility, and not teratogenic.<br>• Tigecycline-related clinical signs (including fur discoloration of the muzzle, pinnae, and/or periorbital area) were present at 12 mg/kg/day.<br>• Decreased body weights were seen in males and females at ≥ 4 and 12 mg/kg/day, respectively.<br>• Decreased mean spermatozoa counts and mean cauda epididymis weights occurred at 12 mg/kg/day without corresponding microscopic findings or effects on reproductive performance.<br>• Decreased fetal weights and reduced ossification occurred at 12 mg/kg/day.<br>• 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.<br>• Increased incidence of fetuses, but not litters, with minor skeletal anomalies at 12 mg/kg/day.<br>• 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. |

**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 |
|---|---|---|---|---|
| Fertility and Developmental Toxicity RPT-42298 (cont'd) | | | | • Mean values for dosages 1, 4, and 12 mg/kg/day, respectively were:<br>GD 6:<br>$C_{5min}$ (mcg/mL):0.97, 4.6, 21<br>$AUC_{0-24}$(mcg•h/mL): 1.79, 7.07, 24.8<br>GD 17:<br>$C_{5min}$ (mcg/mL): 1.78, 10.7, 24.0<br>$AUC_{0-24}$ (mcg•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.<br>• No effects on pregnancy (F0), offspring survival, growth, and development (physical, sensory, behavioral, and reproductive) at dosages producing maternal toxicity (≥4 mg/kg/day).<br>• Maternal (F0) body-weight gain and food consumption were decreased during gestation at ≥ 4 mg/kg/day.<br>• 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.<br>• There was no tigecycline-related mortality. |

**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 |
|---|---|---|---|---|
| Dose-Ranging Developmental Toxicity GTR-33215 (cont'd) | | | pH of the dosing solutions ranged from 7.9 to 8.0 | • Clinical observations consisted of fecal alterations (no feces or diarrhea/loose feces) at all dosages, and 3 animals aborted at 16 mg/kg/day.<br>• 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.<br>• 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.<br>• Gravid uterine weights were decreased 24% and 74% at 4 and 16 mg/kg/day, respectively, compared with controls.<br>• There was an increased incidence of resorptions at 4 and 16 mg/kg/day compared with controls. The post implantation loss was 9% and 50% at 4 and 16 mg/kg/day, respectively, 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.<br>• 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. |

**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 |
|---|---|---|---|---|
| Dose-Ranging Developmental Toxicity GTR-33215 (cont'd) | | | | Mean tigecycline values for dosages 1, 4, and 16 mg/kg/day were, respectively:<br>GD 18:<br>$C_{5min}$ (mcg/mL): 1.05, 8.69, 122<br>$AUC_{0-24}$ (mcg•h/mL): 0.98, 7.45, 93.5.<br>• 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.<br>• Not teratogenic.<br>• 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.<br>• Fetal weights at 4 mg/kg/day were slightly lower (8.3%) than controls.<br>• Increased percentage of fetuses with semi-bipartite thoracic 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.<br>• 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. |

**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 |
|---|---|---|---|---|
| Developmental Toxicity<br>RPT-42304<br>(cont'd) | | | | • Mean tigecycline values for dosages 0.25, 1, and 4 mg/kg/day were, respectively:<br>GD 6:<br>$C_{5min}$ (mcg/mL): 0.289, 1.03, 10.2<br>$AUC_{0-24}$ (mcg•h/mL): 0.220, 1.49, 9.69<br>GD 18:<br>$C_{5min}$ (mcg/mL): 0.318, 1.26, 6.30<br>$AUC_{0-24}$ (mcg•h/mL): 0.206, 1.29, 6.75. |
| **Other Toxicity Studies** | | | | • |
| Antigenicity<br>GTR-33263 | Sensitization:<br>Mice;<br>BALB/c and C3H/He;<br>6F/strain/dose group<br>7 – 9 weeks;<br>14 – 22 g | IV, bolus (needle) or IP; once a week for 3 weeks | 0 (0 mg/mL),<br>3 (3 mg/mL),<br>30 (30 mg/mL);<br>10 mL/kg;<br>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.<br>• Not antigenic as assessed by PCA assay.<br>• Serum histamine levels in rats 10 to 15 minutes after 30 mg/kg IV dose were not biologically significantly increased. |
| | Challenge:<br>Rats; S-D<br>2F/serum sample, 6F;<br>10 weeks;<br>177- 253 g | IV, bolus;<br>1 day | 30;<br>1 mL/kg | |

**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 |
|---|---|---|---|---|
| Antigenicity<br>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.<br>• After IV administration of 3 mg/kg, adverse tigecycline-related clinical signs were twitching, respiratory alterations, erythema, blue extremities.<br>• Recovery was evident at 24 hours.<br>• All other animals appeared normal at every observation period.<br>• Serum histamine levels at 10 to 15 minutes post dose were not increased in available samples (0.3 and 1 mg/mL).<br>• The intolerability observed in this study precluded further studies in this species. |
| Hematotoxicity Recoverability<br>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.<br>• Hematotoxicity of tigecycline was characterized by decreases in RBC parameters, reticulocytes, WBCs, and platelets.<br>• 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.<br>• Slight to moderate (10% to 17 %) body-weight loss.<br>• Increased APTT (up to 86 %) was present in tigecycline treated dogs.<br>• Recovery in all evaluated parameters was evident by the end of a 3-week tigecycline-free period in all tigecycline-treated dogs.<br>• No irreversible tigecycline-related hematotoxicity was evident. |

**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 |
|---|---|---|---|---|
| Phototoxicity Assessment RPT-55059 | Male Rats; Long-Evans; 5M/dosage; ~ 8 weeks; 263 – 284 g | IV, bolus (needle); single dose<br><br>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<br>• Animals were observed up to 3 days post-dose<br>• After IV administration, both dermal and ocular assessments were negative for phototoxicity.<br>• 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<br><br>*Suncus murinus;* 3/dosage | IV, infusion (catheter); single dose<br><br>Oral; single dose | 0, 100, 300, 600; 10 mL/kg; 1 mL/min;<br><br>0, 300, 600, 1000; 10 mL/kg; distilled water | • Evaluations were based on mortality and emesis.<br>• After IV administration, emesis was induced only at a lethal dosage (600 mg/kg).<br>• 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.<br>• 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.<br>• No other hemolysis or protein precipitation was observed in this study.<br>• Tigecycline solutions of 35, 20, and 8 mg/mL were compatible with rat, dog, and human blood, with levels of hemolysis and/or protein precipitation not considered to be toxicologically significant. |

**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 |
|---|---|---|---|---|
| Cellular Protein Synthesis and Mitochondrial Protein Synthesis MIRACL-26519 | Dog Hepatocytes<br><br>Rat and Dog Mitochondrial Suspensions | *In Vitro* | 1 to 100 mcg/mL; 20 hours<br><br>9.4 to 282 mcg/mL; 1 hour | • Did not inhibit cellular protein synthesis.<br>• 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 20, 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.

## 17 SUPPORTING PRODUCT MONOGRAPHS

1. TYGACIL® 50 mg/vial, for intravenous use, submission control 251294, Product Monograph, Pfizer Canada ULC. (AUG 25, 2021)

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

### PrTIGECYCLINE FOR INJECTION

### Tigecycline

Read this carefully before you start taking **TIGECYCLINE FOR INJECTION** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TIGECYCLINE FOR INJECTION**.

### What is TIGECYCLINE FOR INJECTION used for?

**TIGECYCLINE FOR INJECTION** is an antibiotic medicine. It is used to treat the following serious bacterial infections in adults:

- skin infections
- abdomen infections
- community acquired pneumonia (lung infections caught outside of hospitals or other health care facilities)

Antibacterial drugs like **TIGECYCLINE FOR INJECTION** treat only bacterial infections. They do not treat viral infections. Although you may feel better early in treatment, **TIGECYCLINE FOR INJECTION** should be used exactly as directed. Misuse or overuse of **TIGECYCLINE FOR INJECTION** could lead to the growth of bacteria that will not be killed by **TIGECYCLINE FOR INJECTION** (resistance). This means that **TIGECYCLINE FOR INJECTION** may not work for you in the future.

### How does TIGECYCLINE FOR INJECTION work?

**TIGECYCLINE FOR INJECTION** belongs to the class of medicines called tetracycline antibiotics. It works by helping to stop the growth of bacteria responsible for your infection.

### What are the ingredients in TIGECYCLINE FOR INJECTION?

Medicinal ingredient: Tigecycline

Non-medicinal ingredients: L-arginine, hydrochloric acid, sodium hydroxide.

### TIGECYCLINE FOR INJECTION comes in the following dosage forms:

**TIGECYCLINE FOR INJECTION** comes as a powder to be mixed with a specific liquid and injected slowly into a vein.

**TIGECYCLINE FOR INJECTION** is supplied as a 5 mL single-dose glass vial.

Each **TIGECYCLINE FOR INJECTION** vial contains 50 mg of tigecycline powder.

### Do not use TIGECYCLINE FOR INJECTION if:

- you are allergic to tigecycline,
- you are allergic to any other ingredients of **TIGECYCLINE FOR INJECTION** (see **What are the ingredients in TIGECYCLINE FOR INJECTION?**),
- you are allergic to other tetracycline antibiotics such as doxycycline, minocycline, and tetracycline.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TIGECYCLINE FOR INJECTION. Talk about any health conditions or problems you may have, including if you:**

- have other infections.
- have liver problems.
- are pregnant or planning to become pregnant. **TIGECYCLINE FOR INJECTION** may cause fetal harm.
- are breastfeeding or planning to breastfeed. It is not known if tigecycline passes into breast milk. There is a possibility of permanent staining of the teeth of the child.

**Children**

**TIGECYCLINE FOR INJECTION** is for use in adults aged 18 and over. There is no experience with the use of tigecycline in children under 18 years of age. **TIGECYCLINE FOR INJECTION** may cause enamel loss and staining in developing teeth.

**Other warnings you should know about:**

While taking **TIGECYCLINE FOR INJECTION**

- If you develop a racing heartbeat (palpitations) or faint, contact your doctor immediately.
- Do not drive or operate machinery. **TIGECYCLINE FOR INJECTION** may cause side effects such as dizziness.
- Follow your healthcare professional's instructions carefully.
- If your condition does not improve in a few days or if it gets worse, contact your healthcare professional.
- **TIGECYCLINE FOR INJECTION** may make your skin more sensitive to sunlight than it is normally. To protect your skin from sunburn, you should:
    - Wear protective clothing and sunglasses
    - Limit your time in the sun especially between 11 a.m. and 4 p.m.
    - Use sunscreen
    - Avoid using tanning beds
- **TIGECYCLINE FOR INJECTION** may cause a condition in which the pressure inside the skull is increased (Pseudotumor cerebri). If you experience any of these symptoms, call your healthcare professional immediately:
    - Severe headache
    - Buzzing sound in the ears (tinnitus)
    - Severe dizziness
    - Vision changes
    - Severe nausea
- If you develop severe diarrhea during your treatment with **TIGECYCLINE FOR INJECTION** or over 2 months after your treatment is finished, call your healthcare professional immediately (see What are possible side effects from using **TIGECYCLINE FOR INJECTION**? Section below).
- Do not use any medicine to treat your diarrhea without first checking with your doctor.
- Your healthcare professional may order some blood tests for you before and while you are on treatment with **TIGECYCLINE FOR INJECTION**.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with TIGECYCLINE FOR INJECTION:**

- anticoagulants (blood thinners) such as warfarin
- contraceptive pill (birth control pill). Talk to your doctor about the need for an additional method of contraception while receiving **TIGECYCLINE FOR INJECTION**.
- drugs that weaken the immune system such as tacrolimus or cyclosporine. Taking **TIGECYCLINE FOR INJECTION** may lead to increased levels of these drugs in your body. Tell your healthcare professional if you are taking tacrolimus or cyclosporine so that blood levels can be checked before, during and after taking **TIGECYCLINE FOR INJECTION**. The dose of tacrolimus or cyclosporine may be adjusted while you are taking **TIGECYCLINE FOR INJECTION**.

**How to take TIGECYCLINE FOR INJECTION:**

- Your healthcare professional will give **TIGECYCLINE FOR INJECTION** by intravenous infusion (slow drip through a needle into a large vein) over a period of 30 to 60 minutes.

**Usual dose:**

The usual adult dose of **TIGECYCLINE FOR INJECTION** is 100 mg for the first dose, followed by 50 mg every 12 hours.

The length of your treatment depends on the type of infection you have and how your body responds to **TIGECYCLINE FOR INJECTION**.

**Overdose:**

If you think you, or a person you are caring for, have taken too much TIGECYCLINE FOR INJECTION, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

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

**What are possible side effects from using TIGECYCLINE FOR INJECTION?**

These are not all the possible side effects you may have when taking TIGECYCLINE FOR INJECTION. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

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

If you experience symptoms such as severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness, you may have Clostridium difficile colitis (bowel inflammation). If this occurs, stop taking **TIGECYCLINE FOR INJECTION** and contact your healthcare professional immediately.

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| **UNCOMMON** | | | |
| **Injection site reaction** (pain, redness, inflammation) | | √ | |
| **Vein irritations from the injection** (including pain, inflammation, swelling and clotting) | | √ | |
| **Fever** | | √ | |
| **Chills** | | √ | |
| **Chest pain** | | √ | |
| **Decreased platelets** (cells in the blood that help the blood clot)<br>• Unusual bruising or bleeding<br>• Pinpoint red spots on the skin | | √ | |
| **Jaundice** (dark urine, yellowness of skin or eye) | | | √ |
| **Inflammation of the pancreas** (severe upper stomach pain, often with nausea and vomiting) | | | √ |
| **Serious Skin Reactions** (Stevens Johnson syndrome): flu-like symptoms (fever, headache, cough, body aches, etc.) followed by skin blisters or peeling | | | √ |
| **Allergic reactions** (e.g. rash, difficulty breathing, tightening of chest, swelling of lips, tongue or throat, etc.) | | | √ |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

The healthcare professional will store the product under appropriate conditions.

Keep out of reach and sight of children.

**If you want more information about TIGECYCLINE FOR INJECTION:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.pharmaris.com, or by calling 1-866-913-7955.

This leaflet was prepared by Pharmaris Canada Inc.

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