For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

℞ Tigecycline for Injection 50 mg

TYGARAY™

टीगारे

GENERIC NAME
Tigecycline for injection

COMPOSITION

TYGARAY INJECTION
Each vial contains:
Tigecycline..... 50 mg
Excipients.....q.s.

DESCRIPTION[2]
TYGARAY is Yellow to Orange lyophilized powder or cake in clear glass vial sealed with rubber stoppers and flip off seal. Each TYGARAY vial contains 50 mg Tigecycline (Active Ingredient) as lyophilized powder meant for reconstitution for intravenous infusion. The product does not contain preservatives.
Tigecycline is a glycylcycline antibacterial for intravenous infusion. Its empirical formula is $C_{59}H_{39}N_5O_8$, and its molecular weight is 585.65.

INDICATIONS

Treatment
TYGARAY (Tigecycline for injection) is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below for patients 18 years of age and older:

- **Complicated skin and skin structure infections** caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible and resistant isolates), *Streptococcus agalactiae, Streptococcus anginosus grp.* (includes S. anginosus, S. intermedius, and S. constellatus), *Streptococcus pyogenes, Enterobacter cloacae, Klebsiella pneumonia and Bacteroidesfragilis.*
- **Complicated intra-abdominal infections** caused by *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis (vancomycin susceptible isolates only), Staphylococcus aureus (methicillin susceptible and resistant isolates), Streptococcus anginosus grp. (includes S. anginosus, S. intermedius, and S. constellatus), Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens, and Peptostreptococcus micros.*
- **Community-Acquired Bacterial Pneumonia**
  Community-acquired bacterial pneumonia caused by Streptococcus pneumoniae (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila.*

DOSE AND METHOD OF ADMINISTRATION[2]
The recommended dosage regimen for TYGARAY (Tigecycline for injection) is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous (IV) infusions of TYGARAY should be administered over approximately 30 to 60 minutes every 12 hours.

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

The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress.

Patients with Hepatic impairment: No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response (See **PHARMACODYNAMIC AND PHARMACO-KINETIC PROPERTIES, Pharmacokinetic:** ***Special Populations,*** *Hepatic Insufficiency*).

Reconstitution and Method of Administration
Each vial of TYGARAY (Tigecycline for Injection) should be reconstituted with 5.3 mL of 0.9% Sodium Chloride Injection IP, or 5% Dextrose Injection IP, 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. Immediately 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 colour; 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.
Stability and Compatibility
Prior to reconstitution, TYGARAY (Tigecycline for Injection) should be stored below 25°C. Reconstituted solution must be immediately transferred and further diluted for IV infusion. Tigecycline for injection may be stored in the IV bag at room temperature for up to 6 hours, or refrigerated at 2°C 8°C (36° to 46°F) for up to 24 hours.

Compatible intravenous solutions include 0.9% Sodium Chloride Injection IP, and 5% Dextrose Injection IP. When administered through a Y-site, tigecycline for Injection is compatible with the following drugs or diluents; dobutamine, dopamine HCl, Lactated Ringer's, lidocaine HCl, potassium chloride, ranitidine HCl, and theophylline.

USE IN SPECIAL POPULATIONS[1, 2]

- **Pregnancy**

Tigecycline was not teratogenic in the rat or rabbit. In reported preclinical safety studies, ^{14}C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures.
The administration of tigecycline was associated with slight reductions in fetal weights and an increased incidence of minor skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively (28 mcg.hr/mL and 6 mcg.hr/mL at 12 and 4 mg/kg/day). An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.
There are no adequate and well-controlled studies of tigecycline in pregnant women. Tigecycline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- **Lactation**

Results from reported animal studies using ^{14}C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tigecycline is administered to a nursing woman.

- **Pediatric**

Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Because of effects on tooth development, use in patients under 8 years of age is not recommended.

- **Geriatric**

Of the total number of subjects who received tigecycline in phase 3 clinical studies (n=2514), 664 were 65 and over, while 288 were 75 and over, No unexpected overall differences in safety of effectiveness were observed between these subjects and younger subjects. But greater sensitivity to adverse events of some older individuals cannot be ruled out.
No significant difference in tigecycline exposure was observed between healthy elderly subjects and younger subjects following a single 100 mg dose of tigecycline.

- **Hepatic impairment**

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

CONTRAINDICATIONS[1, 2]
TYGARAY (Tigecycline for injection) is contraindicated for use in patients who have known hypersensitivity to tigecycline. Patients hypersensitive to tetracycline class antibiotics may be hypersensitive to tigecycline.

WARNINGS & PRECAUTIONS

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

Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening. Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effects.

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

Mortality Imbalance and Lower Cure Rates in Ventilator-Associated Pneumonia
A trial of patients with hospital acquired pneumonia failed to demonstrate the efficacy of Tigecycline. In this trial, patients were randomized to receive Tigecycline (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. The sub-group of patients with ventilator-associated pneumonia who received Tigecycline had lower cure rates (47.9% versus 70.1% for the clinically evaluable population).

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

Pancreatitis
Acute pancreatitis, including fatal cases, has occurred in association with Tigecycline treatment. The diagnosis of acute pancreatitis should be considered in patients taking Tigecycline who develop clinical symptoms, signs, or laboratory abnormalities suggestive of acute pancreatitis. Cases have been reported in patients without known risk factors for pancreatitis. Patients usually improve after Tigecycline discontinuation. Consideration should be given to the cessation of the treatment with Tigecycline in cases suspected of having developed pancreatitis.

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

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

Tetracycline-Class Effects
Tigecycline should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics. Tigecycline is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of Tigecycline.

Clostridium *difficile* Associated Diarrhea
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including tigecycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

Superinfection
As with other antibacterial drugs, use of Tigecycline may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

Development of Drug-Resistant Bacteria
Prescribing Tigecycline in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

PRECAUTIONS

- **Patients With Intestinal Perforation**

Caution should be exercised when considering tigecycline monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In reported phase III studies in patients with cIAI (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 (Acute Physiology and Chronic Health Evaluation) 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.

Information for Patients
Patients should be counseled that antibacterial drugs including tigecycline should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When tigecycline is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by tigecycline or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic, If this occurs, patients should contact their physician as soon as possible.

DRUG INTERACTIONS[1, 2]
Tigecycline (100 mg followed by 50 mg every 12 hours) and digoxin (0.5 mg followed by 0.25 mg, orally, every 24 hours) were 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 following 6 cytochrome P450 (GYP) isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. Therefore, tigecycline is not expected to alter the metabolism of drugs metabolized by these enzymes. In addition, because tigecycline is not extensively metabolized, clearance of tigecycline is not expected to be affected by drugs that inhibit or induce the activity of these CYP450 isoforms.
In reported *in vitro* studies, no antagonism has been observed between tigecycline and other commonly used antibiotic classes.
Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.

Laboratory Tests
There are no reported drug-laboratory test interactions

UNDESIRABLE EFFECTS[1, 2]
In reported phase III clinical studies, tigecycline was discontinued due to treatment-emergent adverse events in 7% of patients compared to 6% for all comparators. Table below shows the incidence of treatment-emergent adverse events through test of cure reported in ≥2% of patients in these studies regardless of causality.

Incidence (%) of Adverse Events through test of Cure Reported in 2% of Patients Treated in Clinical Studies

Body System Adverse Events	Tigecycline*	Comparators**
Body as a whole		
Abdominal pain	6	4
Abscess	3	3
Asthenia	3	2
Headache	6	7
Infection	8	5

Cardiovascular System		
Phlebitis	3	4
Digestive System		
Diarrhea	12	11
Dyspepsia	2	2
Nausea	26	13
Vomiting	18	9
Hemic and Lymphatic System		
Anemia	4	5
Metabolic and Nutritional		
Alkaline Phosphatase Increased	4	3
Amylase Increased	3	2
Bilirubinemia	2	1
BUN Increased	3	1
Healing Abnormal	4	3
Hypoproteinemia	5	3
SGOT Increased***	4	5
SGPT Increased***	5	5
Nervous System		
Dizziness	3	3
Skin and Appendages		
Rash	3	4

*100 mg initially, followed by 50mg every 12 hours
**Vancomycin/Aztreonam, Imipenem/Cilastatin, Linezolid
***LFT abnormalities in tigecycline-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.

In reported phase III and IV studies, death occurred in 4.0% of patients receiving tigecycline and 3.0% of patients receiving comparator drugs; this difference is not statistically significant and relationship to treatment cannot be established.

In reported phase III clinical studies, infection - related serious adverse events were more frequently reported for subjects treated with tigecycline (7%) vs comparators (6%).Significant differences in sepsis/septic shock with tigecycline (2%) vs comparators (1 %) were observed. Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established.

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

In patients treated for complicated skin and skin structure infections (cSSSI), nausea incidence was 35.0% for tigecycline and 9% for vancomycin/aztreonam; vomiting incidence was 20.0% for tigecycline and 4% for vancomycin/aztreonam. In patients treated for complicated intraabdominal infections (cIAI), nausea incidence was 25% for tigecycline and 21% for imipenem/cilastatin; vomiting incidence was 20% for tigecycline and 15% for imipenem/cilastatin.

In patients treated for community acquired bacterial pneumonia (CABP) nausea incidence was 24% for tigecycline and 8% for levofloxacin; vomiting incidence was 16% for tigecycline and 6% for levofloxacin.

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

The following drug-related adverse events were reported infrequently (<2%) in patients receiving tigecycline in clinical studies:

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

Cardiovascular System: thrombophlebitis

Digestive System: anorexia,jaundice, abnormal stools

*Metabolic/NutritionalSystem:*increased creatinine, hypocalcemia, hypoglycemia, hyponatremia

Special Senses: taste perversion

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

Skin and Appendages: pruritus

*Urogential System:*vaginal moniliasis,vaginitis,leucorrhea

Post marketing Experience

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

- Anaphylaxis/anaphylactoid reactions
- Acute pancreatitis
- Hepatic cholestasis and jaundice

OVERDOSE[1,2]

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

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.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES[1,2]

- **Mechanismof action**

Tigecycline, a glycylcycline, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNAmolecules 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 isnot present in any naturally occurringor semisynthetic tetracycline and imparts certain microbiologic properties totigecycline. In general, Tigecycline is considered bacteriostatic; however, Tigecycline has demonstrated bactericidal activity against isolates of*S. pneumoniae*and *L. pneumophila.*

Antibacterial Spectrum

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

Tigecycline has been shown to be active against most of the following bacteria, both *in vitro* and in clinical infections.

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

Facultative Gram-negative bacteria
Citrobacterfreundii
Enterobactercloacae
Escherichia coli
Haemophilusinfluenzae(beta-lactamase negative isolates)
Klebsillaoxytoca
Klebsiellapneumoniae
Legionella pneumophila

Anaerobic bacteria
Bacteroidesfragilis
Bacteroidesthetaiotaomicron
Bacteroidesuniformis
Bacteroidesvulgatus
Clostridium perfringens
Peptostreptococcus micros

At least 90% of the following bacteria exhibit in vitro minimum inhibitory concentrations (MICs) that are at concentrations that are achievable using the prescribed dosing regimens.

However, the clinical significance of this is unknown because the safety and effectiveness of tigecycline in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical, trials.

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

Facultative Gram-negative bacteria
*Acinetobacterbaumanni**
Aeromonashydrophila
Citrobacterkoseri
Enterobacteraerogenes
Haemophilusinfluenzae (ampicillin-resistant)
Haemophilusparainnuenzae
Pasteurellamultocida
Serratiamarcescens
Stenotrophomonasmaftophilia

Anaerobic bacteria
Bacteroidesdistasonis
Bacteroidesovatus
Peptostreptococcus spp.
Porphyromonas spp.
Prevotella spp.

Other bacteria
Mycobacterium abscessus
Mycobacterium fortuitum

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

- **Pharmacokinetics**

The mean pharmacokinetic parameters of tigecycline after single and multiple intravenous doses based on pooled data from reported clinical pharmacology studies are summarized in table below. Intravenous infusions of tigecycline were administered over approximately 30 to 60 minutes.

Mean CV%Pharmacokinetic Parameters of Tigecycline		
	Single Dose 100 mg	Multiple Dose* 50 mg q12h
C_{max} (µg/mL)**	1.45 (22%)	0.87 (27%)
C_{min} (µg/mL)***	0.90 (30%)	0.63 (15%)
AUC (µg ·h/mL)	5.19 (36%)	--
AUC_{0-24h} (µg ·h/mL)	--	4.70 (36%)
C_{max}(µg/mL)	--	0.13 (59%)
$t_{½}$	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%)

*100 mg initially, followed by 50 mg every 12 hours
** 30-minute infusion
*** 60-minute infusion

Distribution

The *in vitro* plasma protein binding of tigecycline ranges from approximately 71% to 89% at concentrations observed in reported clinical studies (0.1 to 1.0µg/mL). The steady-state volume of distribution of tigecycline averaged 500 to 700 L (7 to 9 L/kg), indicating tigecycline is extensively distributed beyond the plasma volume and into the tissues.

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

In a single-dose study, tigecycline 100 mg was administered to subjects prior to undergoing elective surgery or medical procedure for tissue extraction. Concentrations at 4 hours after tigecycline administration were higher in gallbladder (38-fold), lung (3.7-fold) and colon (2.3-fold) and lower in synovial fluid (0.58-fold) and bone (0.35-fold) relative to serum. 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 hepatocyles 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 tigecyclineepimer (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. Approximately 22% of the total dose is excreted as unchanged tigecycline in urine.

Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline and its metabolites. Glucuronidation and renal excretion of unchanged tigecycline are secondary routes.

Special Populations

Hepatic Insufficiency:

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

Systematic clearance of tigecycline was reduced by 55%, and the half-life of tigecycline was prolonged by 43% in patients with severe hepatic impairment (Child Pugh C). 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 initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response.

Renal Insufficiency:

A reported single dose study compared subjects with severe renal impairment (creatinine clearance <30 mL/min), end stage renal disease (ESRD) patients receiving tigecycline 2 hour before hemodialysis, ESRD patients receiving tigecycline 1 hour after hemodialysis, and healthy control subjects. The pharmacokinetic profile of tigecycline was not significantly altered in any of the renally impaired patient groups, nor was tigecycline removed by hemodialysis. No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Pediatric:

The pharmacokinetics of tigecycline in patients less than 18 years of age have not been established.

Geriatric:

No significant differences in pharmacokinetics were reported between healthy elderly subjects (age 65-75: age >75) and younger subjects receiving a single 100mg dose of tigecycline. Therefore, no dosage adjustment is necessary based on age.

Gender:

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

Race:

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

INCOMPATIBILITIES

The following drugs should not be administered simultaneously through the same Y-site as TYGARAY (Tigecycline for injection): amphotericin B, chlorpromazine, methylprednisolone, and voriconazole.

SHELF LIFE

Not more than 18 months. Please see Mfg. Date/Expiry Date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

PACKAGING INFORMATION

Supplied in a single-dose tubular glass vial sealed with rubber stopper and flip off seal, containing 50 mg lyophilized powder of TYGARAY (Tigecycline for Injection) for reconstitution.
Supplied as each vial in mono carton.

STORAGE AND HANDLING INSTRUCTIONS

Prior to reconstitution, TYGARAY (Tigecycline for Injection) should be storedbelow 25°C. Reconstituted solution must be immediately transferred and further diluted for I.V. infusion. TYGARAY may be stored in the IV bag at room temperature for up to 6 hours, or refrigerated at 2° to 8°C (36° to 46°F) for up to 24 hours. Do not freeze.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN

REFERENCES

1. US Prescribing Information of **TYGACIL®**, Wyeth Pharmaceuticals Inc., Philadelphia, March 2009
2. UK Summaryof product characteristics of Tygacil 50 mg powder for solution for infusion, Wyeth Pharmaceuticals, July 2009.

Information compiled in November 2009

Marketed & Manufactured by:

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Works:

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