Attachment C

TYGACIL™

(tigecycline)
for injection

℞ **only**

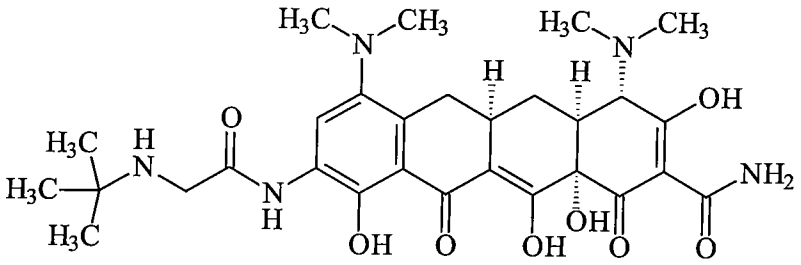
This product's label may have been revised after this insert was used in production. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

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

DESCRIPTION

TYGACIL (tigecycline) is a glycylcycline antibacterial for intravenous infusion. The chemical name of tigecycline is (4*S*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide. The empirical formula is $C_{29}H_{39}N_5O_8$ and the molecular weight is 585.65.

The following represents the chemical structure of tigecycline:



TYGACIL is an orange lyophilized powder or cake. Each TYGACIL vial contains 50 mg tigecycline lyophilized powder for intravenous infusion. The product does not contain excipients or preservatives.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The mean pharmacokinetic parameters of tigecycline after single and multiple intravenous doses based on pooled data from clinical pharmacology studies are summarized in Table 1. Intravenous infusions of tigecycline were administered over approximately 30 to 60 minutes.

Table 1. Mean (CV%) Pharmacokinetic Parameters of Tigecycline

	Single Dose 100 mg (N=224)	Multiple Dose[a] 50 mg q12h (N=103)
C_{max} (μg/mL)[b]	1.45 (22%)	0.87 (27%)
C_{max} (μg/mL)[c]	0.90 (30%)	0.63 (15%)
AUC (μg·h/mL)	5.19 (36%)	- -
$AUC_{0\text{-}24h}$ (μg·h/mL)	- -	4.70 (36%)
C_{min} (μg/mL)	- -	0.13 (59%)
$t_{½}$ (h)	27.1 (53%)	42.4 (83%)
CL (L/h)	21.8 (40%)	23.8 (33%)
CL_r (mL/min)	38.0 (82%)	51.0 (58%)
V_{ss} (L)	568 (43%)	639 (48%)

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

Distribution

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

Following the administration of tigecycline 100 mg followed by 50 mg every 12 hours to 33 healthy volunteers, the tigecycline $AUC_{0\text{-}12h}$ (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 $AUC_{0\text{-}12h}$ (1.61 μg·h/mL) of tigecycline in skin blister fluid was approximately 26% lower than the $AUC_{0\text{-}12h}$ in the serum of 10 healthy subjects.

In a single-dose study, tigecycline 100 mg was administered to subjects prior to undergoing elective surgery or medical procedure for tissue extraction. Concentrations at 4 hours after tigecycline administration were higher in gallbladder (38-fold, n=6), lung (8.6-fold, n=1), and colon (2.1-fold, n=5), and lower in synovial fluid (0.58-fold, n=5), and bone (0.35-fold, n=6) relative to serum. The concentration of tigecycline in these tissues after multiple doses has not been studied.

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. 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

Use in Patients with Hepatic Impairment

In a study comparing 10 patients with mild hepatic impairment (Child Pugh A), 10 patients with moderate hepatic impairment (Child Pugh B), and 5 patients with severe hepatic impairment (Child Pugh C) to 23 age and weight matched healthy control subjects, the single-dose pharmacokinetic disposition of tigecycline was not altered in patients with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25% and the half-life of tigecycyline was prolonged by 23% in patients with moderate hepatic impairment (Child Pugh B). Systemic clearance of tigecycline was reduced by 55%, and the half-life of tigecycline was prolonged by 43% in patients with severe hepatic impairment (Child Pugh C). 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 TYGACIL 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 **PRECAUTIONS, Use in Patients with Hepatic Impairment** and **DOSAGE AND ADMINISTRATION.**)

Use in Patients with Renal Impairment

A single dose study compared 6 subjects with severe renal impairment (creatinine clearance <30 mL/min), 4 end stage renal disease (ESRD) patients receiving tigecycline 2 hours before hemodialysis, 4 ESRD patients receiving tigecycline 1 hour after hemodialysis, and 6 healthy control subjects. The pharmacokinetic profile of tigecycline was not significantly altered in any of the renally impaired patient groups, nor was tigecycline removed by hemodialysis. No dosage adjustment of TYGACIL is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Pediatric Use

The pharmacokinetics of tigecycline in patients less than 18 years of age have not been established. (See **PRECAUTIONS, Pediatric Use.**)

Geriatric Use

No significant 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 TYGACIL. Therefore, no dosage adjustment is necessary based on age. (See **PRECAUTIONS, Geriatric Use.)**

Gender

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

Race

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

Drug-drug Interactions

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

Concomitant administration of TYGACIL (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single-dose) to healthy subjects resulted in a decrease in clearance of R-warfarin and S-warfarin by 40% and 23%, an increase in C_{max} by 38% and 43% and an increase in AUC by 68% and 29%, respectively. Tigecycline did not significantly alter the effects of warfarin on INR. In addition, warfarin did not affect the pharmacokinetic profile of tigecycline. However, prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin.

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

Microbiology

Tigecycline, a glycylcycline, 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 to tigecycline. Tigecycline is not affected by 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. Tigecycline is not affected by resistance mechanisms such as beta-lactamases (including extended spectrum beta-lactamases), target site modifications, macrolide efflux pumps or enzyme target changes (e.g. gyrase/topoisomerase). In vitro studies have not demonstrated antagonism between tigecycline and other commonly used antibacterial drugs. In general, tigecycline is considered bacteriostatic.

Tigecycline has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic facultative Gram-positive microorganisms

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

Aerobic and facultative Gram-negative microorganisms

Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae

Anaerobic microorganisms

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

The following in vitro data are available, **but their clinical significance is unknown.** At least 90% of these microorganisms exhibit in vitro minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoint for tigecycline. However, the safety and effectiveness of tigecycline in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms

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

Aerobic and facultative Gram-negative microorganisms

Acinetobacter baumannii
Aeromonas hydrophila
Citrobacter koseri
Enterobacter aerogenes
Pasteurella multocida
Serratia marcescens
Stenotrophomonas maltophilia

Anaerobic microorganisms

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

Other microorganisms

Mycobacterium abscessus
Mycobacterium chelonae
Mycobacterium fortuitum

Susceptibility Test Methods

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

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)[1,3,4] or equivalent using standardized inoculum and concentrations of tigecycline. For broth dilution tests for aerobic organisms, MICs must be determined in testing medium that is fresh (<12h old). The MIC values should be interpreted according to the criteria provided in Table 2.

Diffusion techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The standardized procedure[2,4] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 μg tigecycline to test the susceptibility of microorganisms to tigecycline. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for tigecycline. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 μg tigecycline disk should be interpreted according to the criteria in Table 2.

Anaerobic techniques

Anaerobic susceptibility testing with tigecycline should be done by the agar dilution method[3] since quality control parameters for broth-dilution are not established.

Table 2. Susceptibility Test Result Interpretive Criteria for Tigecycline

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

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

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

Quality Control

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures.[1,2,3,4] Standard tigecycline powder should provide the MIC values provided in Table 3. For the diffusion technique using the 15 μg tigecycline disk the criteria provided in Table 3 should be achieved.

Table 3. Acceptable Quality Control Ranges for Susceptibility Testing

QC organism	Minimum Inhibitory Concentrations (μg/mL)	Disk Diffusion (zone diameters in mm)
Staphylococcus aureus ATCC 25923	Not Applicable	20-25
Staphylococcus aureus ATCC 29213	0.03-0.25	Not Applicable
Escherichia coli ATCC 25922	0.03-0.25	20-27
Enterococcus faecalis ATCC 29212	0.03-0.12	Not Applicable
Bacteroides fragilis[a] ATCC 25285	0.12-1	Not Applicable
Bacteroides thetaiotaomicron[a] ATCC 29741	0.5-2	Not Applicable
Eubacterium lentum[a] ATCC 43055	0.06-0.5	Not Applicable

ATCC = American Type Culture Collection
[a] Agar dilution

INDICATIONS AND USAGE

TYGACIL 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* and *Bacteroides fragilis.*

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 isolates 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.*

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYGACIL and other antibacterial drugs, TYGACIL 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.

CONTRAINDICATIONS

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

WARNINGS

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effects.

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

The use of TYGACIL 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 TYGACIL have shown bone discoloration. TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.

TYGACIL should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics.

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

Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis." After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

General

Caution should be exercised when considering TYGACIL monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. (See **ADVERSE REACTIONS.**) In Phase 3 cIAI studies (n=1642), 6 patients treated with TYGACIL and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with TYGACIL 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.

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

As with other antibacterial drugs, use of TYGACIL 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.

Prescribing TYGACIL 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.

Information for Patients

Patients should be counseled that antibacterial drugs including TYGACIL should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When TYGACIL 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 TYGACIL or other antibacterial drugs in the future.

Drug Interactions

Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions.**)

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

Drug/Laboratory Test Interactions

There are no reported drug-laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy

Teratogenic Effects—Pregnancy Category D

Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, ^{14}C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of tigecycline was associated with 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. 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. TYGACIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS.**)

Labor and Delivery

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

Nursing Mothers

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

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TYGACIL is administered to a nursing woman. (See **WARNINGS.**)

Use in Patients with Hepatic Impairment

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

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established. (See **WARNINGS.**) Therefore, use in patients under 18 years of age is not recommended.

Geriatric Use

Of the total number of subjects who received TYGACIL in Phase 3 clinical studies (n=1415), 278 were 65 and over, while 110 were 75 and over. No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

ADVERSE REACTIONS

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

Phase 3 clinical studies enrolled 1415 patients treated with TYGACIL. TYGACIL was discontinued due to treatment-emergent adverse events in 5.0% of patients compared to 4.7% for all comparators (5.3% for vancomycin/aztreonam and 4.4% for imipenem/cilastatin). Table 4 shows the incidence of treatment-emergent adverse events through test of cure reported in ≥2% of patients in these studies regardless of causality.

Table 4. Incidence (%) of Treatment-Emergent Adverse Events Through Test of Cure Reported in ≥2% of Patients Treated in Phase 3 Clinical Studies

Body System Adverse Events	TYGACIL[a] (N=1415)	Comparators[b] (N=1382)
Body as a Whole		
Abdominal pain	6.8	5.7
Abscess	3.2	2.6
Asthenia	2.5	1.7
Back Pain	1.2	2.3
Fever	7.1	9.8
Headache	5.9	6.5
Infection	8.3	5.4
Pain	3.7	2.9
Cardiovascular System		
Hypertension	4.9	5.6
Hypotension	2.3	1.7
Phlebitis	1.8	3.8
Digestive System		
Constipation	2.8	4.1
Diarrhea	12.7	10.8
Dyspepsia	2.9	1.6
Nausea	29.5	15.8
Vomiting	19.7	10.8
Hemic and Lymphatic System		
Anemia	4.2	4.8
Leukocytosis	3.7	2.5
Thrombocythemia	6.1	6.2
Metabolic and Nutritional		
Alkaline Phosphatase Increased	3.5	2.6
Amylase Increased	3.1	1.4
Bilirubinemia	2.3	0.9
BUN Increased	2.1	0.2
Healing Abnormal	3.5	2.6
Hyperglycemia	1.8	2.9
Hypokalemia	2.1	2.9
Hypoproteinemia	4.5	3.0
Lactic Dehydrogenase Increased	4.0	3.5
Peripheral Edema	3.3	3.3
SGOT Increased[c]	4.3	4.4
SGPT Increased[c]	5.6	4.7
Nervous System		
Dizziness	3.5	2.7
Insomnia	2.3	3.3
Respiratory System		
Cough Increased	3.7	3.8
Dyspnea	2.9	2.7
Pulmonary Physical Finding	1.9	2.2
Skin and Appendages		
Pruritus	2.6	4.1
Rash	2.4	4.1
Sweating	2.3	1.6
Other		
Local Reaction to Procedure	9.0	9.1

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] Vancomycin/Aztreonam, Imipenem/Cilastatin, Linezolid

Table 4. Incidence (%) of Treatment-Emergent Adverse Events Through Test of Cure Reported in ≥2% of Patients Treated in Phase 3 Clinical Studies

[c] LFT abnormalities in TYGACIL-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.

In Phase 3 cSSSI and cIAI studies, death occurred in 2.3% (32/1383) of patients receiving TYGACIL and 1.6% (22/1375) of patients receiving comparator drugs; this difference is not statistically significant and relationship to treatment cannot be established. In all treatment groups, mortality was associated with higher baseline co-morbidity and/or greater severity of baseline infections.

In Phase 3 clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with TYGACIL (6.7%) vs comparators (4.6%). Significant differences in sepsis/septic shock with TYGACIL (1.5%) vs comparators (0.5%) were observed. Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established. (See **PRECAUTIONS**.) Other events included nonsignificant differences in abscess (1.8% vs 1.6%) and infections, including wound infections (1.7% vs 1.1%) for TYGACIL vs comparators, respectively.

The most common treatment-emergent adverse events, were nausea and vomiting which generally occurred during the first 1 – 2 days of therapy. The majority of cases of nausea and vomiting associated with TYGACIL and comparators were either mild or moderate in severity. In patients treated with TYGACIL, nausea incidence was 29.5% (19.6% mild, 8.5% moderate, 1.4% severe) and vomiting incidence was 19.7% (12.3% mild, 6.3% moderate, 1.1% severe). In patients treated for complicated skin and skin structure infections (cSSSI), nausea incidence was 35.0% for TYGACIL and 8.9% for vancomycin/aztreonam; vomiting incidence was 20.0% for TYGACIL and 4.2% for vancomycin/aztreonam. In patients treated for complicated intra-abdominal infections (cIAI), nausea incidence was 25.3% for TYGACIL and 20.5% for imipenem/cilastatin; vomiting incidence was 19.5% for TYGACIL and 15.3% for imipenem/cilastatin.

Discontinuation from tigecycline was most frequently associated with nausea (1.3%) and vomiting (1.0%). For comparators, discontinuations were most frequently associated with rash (1.1%, vancomycin/aztreonam) and nausea (1.0%, imipenem/cilastatin).

The following drug-related adverse events were reported infrequently (≥0.2% and <2%) in patients receiving TYGACIL in Phase 3 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, bradycardia, tachycardia, vasodilatation
Digestive System: anorexia, dry mouth, jaundice, abnormal stools
Metabolic/Nutritional System: increased creatinine, hypocalcemia, hypoglycemia, hyponatremia
Nervous System: somnolence
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
Urogenital System: vaginal moniliasis, vaginitis, leukorrhea

OVERDOSAGE

No specific information is available on the treatment of overdosage with tigecycline. Intravenous administration of TYGACIL 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.

DOSAGE AND ADMINISTRATION

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

The recommended duration of treatment with TYGACIL for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 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.

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 TYGACIL should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response. (See **CLINICAL PHARMACOLOGY, Special Populations**, Use in Patients with Hepatic Impairment and **PRECAUTIONS, Use in Patients with Hepatic Impairment**.)

No dosage adjustment of TYGACIL is necessary in patients with renal impairment or in patients undergoing hemodialysis. (See **CLINICAL PHARMACOLOGY, Special Populations**, Use in Patients with Renal Impairment.)

No dosage adjustment of TYGACIL is necessary based on age, gender, or race. (See **CLINICAL PHARMACOLOGY, Special Populations** and **PRECAUTIONS, Geriatric Use.**)

Preparation and Handling

Each vial of TYGACIL should be reconstituted with 5.3 mL of 0.9% Sodium Chloride Injection, USP, or 5% Dextrose 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. 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 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. TYGACIL 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.

TYGACIL 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 TYGACIL with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. Injection should be made with an infusion solution compatible with tigecycline and with any other drug(s) administered via this common line. (See **DOSAGE AND ADMINISTRATION, Preparation and Handling,** Compatibilities/Incompatibilities.)

Compatibilities/Incompatibilities

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

The following drugs should not be administered simultaneously through the same Y-site as TYGACIL: amphotericin B, chlorpromazine, methylprednisolone, and voriconazole.

HOW SUPPLIED

TYGACIL (tigecycline) for injection is supplied in a single-dose 5 mL glass vial containing 50 mg lyophilized powder for reconstitution.

Supplied 10 vials/box. NDC: 0008-5360-02

Storage

Prior to reconstitution, TYGACIL should be stored at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.] Reconstituted solution must be immediately transferred and further diluted for I.V. infusion. TYGACIL 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.

ANIMAL TOXICOLOGY

In two week studies, decreased erythrocytes, reticulocytes, leukocytes, and platelets, in association with bone marrow hypocellularity, have been seen with tigecycline at exposures of 8 times and 10 times the human daily dose based on AUC in rats and dogs, respectively. These alterations were shown to be reversible after two weeks of dosing.

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

CLINICAL STUDIES

Complicated Skin and Skin Structure Infections

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

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

	TYGACIL[a] n/N (%)	Vancomycin/Aztreonam[b] n/N (%)
Integrated		
CE	365/422 (86.5)	364/411 (88.6)
c-mITT	429/538 (79.7)	425/519 (81.9)
Study 300		
CE	165/199 (82.9)	163/198 (82.3)
c-mITT	209/277 (75.5)	200/260 (76.9)
Study 305		
CE	200/223 (89.7)	201/213 (94.4)
c-mITT	220/261 (84.3)	225/259 (86.9)

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

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

Pathogen	TYGACIL n/N (%)	Vancomycin/Aztreonam n/N (%)
Escherichia coli	27/32 (84.4)	26/30 (86.7)
Enterococcus faecalis (vancomycin-susceptible only)	13/17 (76.5)	24/29 (82.8)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	125/139 (89.9)	118/126 (93.7)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	29/37 (78.4)	26/34 (76.5)
Streptococcus agalactiae	8/8 (100)	11/13 (84.6)
Streptococcus anginosus grp.[b]	16/20 (80.0)	9/10 (90.0)
Streptococcus pyogenes	31/33 (93.9)	24/27 (88.9)
Bacteroides fragilis	6/8 (75.0)	4/5 (80.0)

[a] Two cSSSI pivotal studies and one Phase 3 Resistant Pathogen study
[b] Includes *Streptococcus anginosus, Streptococcus intermedius,* and *Streptococcus constellatus*

Complicated Intra-abdominal Infections

TYGACIL was evaluated in adults for the treatment of complicated intra-abdominal infections (cIAI) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 301 and 306). These studies compared TYGACIL (100 mg IV initial dose followed by 50 mg every 12 hours) with imipenem/cilastatin (500 mg IV every 6 hours) for 5 to 14 days. Patients with complicated diagnoses including appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis were enrolled in the studies. The primary efficacy endpoint was the clinical response at the TOC visit for the co-primary populations of the microbiologically evaluable (ME) and the microbiologic modified intent-to-treat (m-mITT) patients. See Table 7. Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 8.

Table 7. Clinical Cure Rates from Two Pivotal Studies in Complicated Intra-abdominal Infections after 5 to 14 Days of Therapy

	TYGACIL[a] n/N (%)	Imipenem/Cilastatin[b] n/N (%)
Integrated		
ME	441/512 (86.1)	442/513 (86.2)
m-mITT	506/631 (80.2)	514/631 (81.5)
Study 301		
ME	199/247 (80.6)	210/255 (82.4)
m-mITT	227/309 (73.5)	244/312 (78.2)
Study 306		
ME	242/265 (91.3)	232/258 (89.9)
m-mITT	279/322 (86.6)	270/319 (84.6)

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

Table 8. Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Complicated Intra-abdominal Infections[a]

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

[a] Two cIAI pivotal studies

[b] Includes *Streptococcus anginosus, Streptococcus intermedius,* and *Streptococcus constellatus*

REFERENCES

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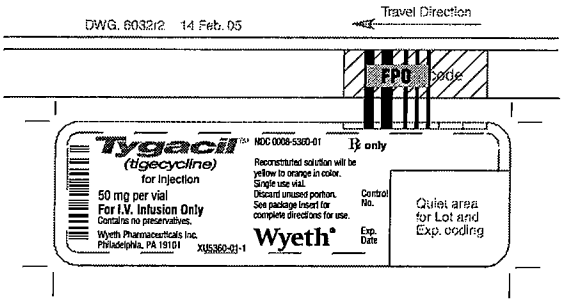
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