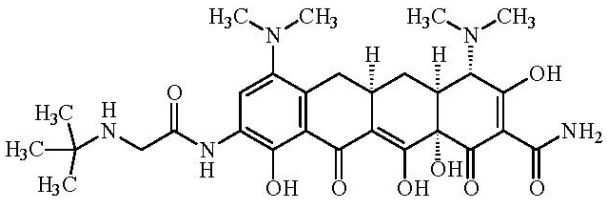
PT Pfizer Indonesia
Local Product Document
Generic Name: Tigecycline
Trade Name: **TYGACIL™**
CDS Effective Date: December 01, 2020
Supersedes: November 15, 2019

℞ only

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. Each vial contains 100 mg of lactose monohydrate. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide.

CLINICAL PHARMACOLOGY

Anti-infective
Glycylcycline antibacterial
ATC code: J01C XXX

Pharmacokinetics

The mean pharmacokinetic parameters of tigecycline after single and multiple intravenous doses 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	Multiple Dose[a] 50 mg q 12h
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%)

$t_{1/2}$ (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

Absorption
Tigecycline is administered intravenously, and therefore has 100% bioavailability.

Distribution
The *in vitro* plasma protein binding of tigecycline ranges from approximately 71% to 89% at concentrations observed in clinical studies (0.1 to 1.0 μg/mL). Animal and human pharmacokinetic studies have demonstrated that tigecycline readily distributes to tissues. In rats receiving single or multiple doses of ^{14}C-tigecycline, radioactivity was well distributed to most tissues, with the highest overall exposure observed in bone, bone marrow, thyroid gland, kidney, spleen, and salivary gland. In humans, the steady-state volume of distribution of tigecycline averaged 500 to 700 L (7 to 9 L/kg), indicating tigecycline is extensively distributed beyond the plasma volume and into the tissues of humans.

Two studies examined the steady-state pharmacokinetic profile of tigecycline in specific tissues or fluids of healthy subjects receiving tigecycline 100 mg followed by 50 mg every 12 hours. In a bronchoalveolar lavage study, the tigecycline $AUC_{0\text{-}12h}$ (134 μg·h/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 μg·h/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 μg·h/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 (3.7-fold, n=5), and colon (2.3-fold, n=6). 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. 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
Use in Patients with Hepatic Impairment
In a study comparing 10 subjects with mild hepatic impairment (Child Pugh A), 10 subjects with moderate hepatic impairment (Child Pugh B), and 5 subjects 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 subjects with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25%, and the half-life of tigecycline was prolonged by 23% in subjects with moderate hepatic impairment (Child Pugh B). In addition, systemic clearance of tigecycline was reduced by 55%, and the half-life of tigecycline was prolonged by 43% in subjects with severe hepatic impairment (Child Pugh C).

Based on the pharmacokinetic profile of tigecycline, no dosage adjustment is warranted in subjects with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). However, in subjects with severe hepatic impairment (Child Pugh C), the dose of **TYGACIL** should be reduced to 100 mg followed by 25 mg every 12 hours. Subjects 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 subjects receiving tigecycline 2 hours before hemodialysis, 4 end stage renal disease subjects receiving tigecycline 1 hour after hemodialysis, and 6 healthy control subjects. The pharmacokinetic profile of tigecycline was not altered in any of the renally impaired subject groups, nor was tigecycline removed by hemodialysis. No dosage adjustment of **TYGACIL** is necessary in subjects with renal impairment or in subjects undergoing hemodialysis (See **DOSAGE AND ADMINISTRATION**).

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 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 **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 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%, and 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 increased international normalized ratio (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 CYP450 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 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 above.

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.

Concomitant use of tigecycline and calcineurin inhibitors such as tacrolimus or cyclosporine may lead to an increase in serum trough concentrations of the calcineurin inhibitors. Therefore, serum concentrations of the calcineurin inhibitor should be monitored during treatment with tigecycline to avoid drug toxicity.

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. At 4 times the minimum inhibitory concentration (MIC), a 2-log reduction in colony counts was observed with tigecycline against *Enterococcus spp*., *Staphylococcus aureus*, and *Escherichia coli.* However, tigecycline has demonstrated bactericidal activity against common respiratory strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Legionella pneumophila*.

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 and facultative gram-positive microorganisms
Enterococcus faecalis (vancomycin-susceptible isolates only)
Staphylococcus aureus (methicillin-susceptible and -resistant isolates including isolates that bear molecular and virulence markers commonly associated with community-acquired MRSA including the SCCmec type IV element and the pvl gene)
Streptococcus agalactiae
Streptococcus anginosus grp. (includes S. anginosus, S. intermedius, and S. constellatus)
Streptococcus pneumoniae (penicillin-susceptible isolates)

Streptococcus pyogenes

Aerobic and facultative gram-negative microorganisms
Citrobacter freundii
Enterobacter cloacae
Escherichia coli (include ESBL, producing isolates)
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae (including ESBL, producing isolate)
Legionella pneumophila
Moraxella catarrhalis

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

Other microorganism
Chlamydia pneumoniae
Mycoplasma pneumoniae

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 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
Streptococcus pneumoniae (penicillin-resistant isolates)
Viridans group streptococci

Aerobic gram-negative microorganisms
Acinetobacter calcoaceticus/baumannii complex
Aeromonas hydrophila
Citrobacter koseri
Enterobacter aerogenes

Haemophilus parainfluenzae
Neisseria meningitidis
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

Resistance:
There has been no cross-resistance observed between tigecycline and other antibiotics caused by antibiotic-specific resistance mechanisms.

Tigecycline is not affected by the major tetracycline resistance mechanism of ribosomal protection and is not affected by many efflux systems.

In in vitro studies, no antagonism has been observed between tigecycline and any other commonly used antibiotic class.

Susceptibility Tests
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 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 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 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.

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	-	-
Streptococcus pneumoniae	≤ 0.12[a]	-	-	≥ 21	-	-
Enterococcus faecalis (vancomycin-susceptible isolates only)	≤ 0.25[a]	-	-	≥ 19	-	-
Enterobacteriaceae[b]	≤ 2	4	≥ 8	≥ 19	15-18	≤ 14
Haemophilus influenzae	≤ 0.1[a]	-	-	≥ 21	-	-
Moraxella catarrhalis	≤ 0.12[a]	-	-	≥ 27	-	-
Anaerobes[c]	≤ 4	8	≥ 16	n/a	n/a	n/a

S= Susceptible; I=Intermediate; R=Resistant

[a]The current absence of resistance 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. Standard tigecycline powder should provide the MIC values provided in Table 3. For the diffusion technique using the 15 μg tigecycline disk, laboratories should use the criteria provided in Table 3 to test quality control strains.

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
Streptococcus pneumoniae ATCC 49619	0.016-0.12	23-29
H. influenzae ATCC 49247	0.06-0.5	23-31
Bacteroides fragilis ATCC 25285	0.12 – 1	Not Applicable
Bacteroides thetaiotaomicron ATCC 29741	0.5 – 2	Not Applicable
Eubacterium lentum ATCC 43055	0.06 – 0.5	Not Applicable
Clostridium difficile ATCC 70057	0.12-1	Not Applicable

ATCC = American Type Culture Collection

INDICATIONS AND USAGE

TYGACIL is indicated for the treatment of the following infections caused by susceptible strains of the designated microorganisms:

Complicated skin and skin structure infections (cSSSI) caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), including cases with concurrent bacteremia, *Streptococcus agalactiae, Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis.*

Complicated intra-abdominal infections (cIAI) caused by *Citrobacter freundii, Enterobacter cloacae, Escherichia coli* (includes ESBL producing isolates)*, Klebsiella oxytoca, Klebsiella pneumoniae* (includes ESBL producing isolates)*, Enterococcus*

faecalis (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), including cases with concurrent bacteremia, *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

An increase in all-cause mortality has been observed across phase 3 and 4 clinical studies in TYGACIL treated subjects versus comparator-treated subjects. In a pooled analysis of all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of subjects receiving tigecycline and 3.0% (110/3646) of subjects receiving comparator drugs resulting in an unadjusted risk difference of 0.9% (95% CI 0.1, 1.8). 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 subjects. The cause of this increase has not been established. This increase should be considered when selecting among treatment options (See **PRECAUTIONS** and **ADVERSE REACTIONS**).

Anaphylactic reaction/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. Therefore, **TYGACIL** should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics. Due to the structural similarities of glycylcycline class antibiotics to tetracycline class antibiotics, similar adverse effects may include: photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia).

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.

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 diarrhoea 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 tigecycline monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In Phase 3 and 4 cIAI studies (n=2775), 140/1382 tigecycline-treated patients and 142/1393 comparator-treated patients presented with intestinal perforations. Of these patients, 8/140 patients treated with tigecycline and 8/142 patients treated with comparator developed sepsis/septic shock. The relationship of this outcome to treatment cannot be established.

Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline.

Pancreatitis acute, which can be fatal, has occurred (frequency: uncommon) in association with tigecycline treatment (See **ADVERSE REACTIONS**). The diagnosis of pancreatitis acute should be considered in patients taking tigecycline who develop clinical symptoms, signs, or laboratory abnormalities suggestive of pancreatitis acute. 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 subjects suspected of having developed pancreatitis.

Monitoring of blood coagulation parameters, including blood fibrinogen, is recommended prior to treatment initiation with tigecycline and regularly while on treatment (See **ADVERSE REACTIONS**).

The safety and efficacy of tigecycline in patients with hospital acquired pneumonia (HAP) have not been established. In a study of subjects with HAP, subjects were randomized to receive tigecycline (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, subjects were allowed to receive specified adjunctive therapies. The sub-group of subjects 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 14/122 [11.5%]) than the comparator. Of those subjects 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.

As with other antibiotic preparations, use of this medicinal product 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 or a prophylactic indication 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 antibiotics with oral contraceptives may render oral contraceptives less effective.

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

Effect on Activities Requiring Concentration and Performance
Tigecycline can cause dizziness (See **ADVERSE REACTIONS**), which may impair the ability to drive and/or operate machinery.

Carcinogenesis, Mutagenesis, Reproduction Toxicity
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 micronucleus assay. Tigecycline did not affect mating or fertility in rats at exposures up to 4.7 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 4.7 times the human daily dose based on AUC.

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 4.7 times and 1.1 times the human daily dose based on AUC in rats and rabbits, respectively.

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 the nursing pups as a result of exposure via the maternal milk.

Pregnancy
Teratogenic Effects – Pregnancy Category C
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. Decreased fetal weights in rats and rabbits (with associated delays in ossification) have been observed with tigecycline.

Tigecycline was not teratogenic in the rat or rabbit (See **PRECAUTIONS, Carcinogenesis, Mutagenesis, Reproduction Toxicity**).

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.

Lactation
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 **PRECAUTIONS, Carcinogenesis, Mutagenesis, Reproduction Toxicity**). Because many drugs are excreted in human milk, caution should be exercised when **TYGACIL** is administered to a nursing woman (See **WARNINGS**).

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 (See **PRECAUTIONS, Carcinogenesis, Mutagenesis, Reproduction Toxicity**).

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 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 **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 have not been established (See **WARNINGS**). Therefore, use in patients under 18 years of age is not recommended.

Geriatric Use
In a pooled analysis of 3900 subjects who received tigecycline in Phase 3 and 4 clinical studies, 1026 were 65 and over. Of these, 419 were 75 and over. No unexpected overall differences in safety were observed between these subjects and younger subjects. No dosage adjustment is necessary in elderly patients.

ADVERSE REACTIONS

Expected frequency of adverse reactions is presented in CIOMS frequency categories:

Very common	≥10%
Common	≥1% and <10%
Uncommon	≥0.1% and <1%
Rare	≥0.01% and <0.1%
Very rare	< 0.01%
Frequency not known	cannot be estimated from the available data

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

In Phase 3 clinical studies 2514 patients were treated with **TYGACIL**. **TYGACIL** was discontinued due to adverse events in 5.0% of patients compared to 4.7% for all comparators. Table 4 shows the incidence of treatment-emergent adverse reactions reported in ≥ 2% of patients in these studies.

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

Body System Adverse Events	**TYGACIL**[a] (N = 2514)	**Comparator**[b] (N = 2307)
Body as a Whole		
Abdominal pain	6.0	4.4
Headache	6.0	6.7
Cardiovascular System		
Phlebitis	2.5	4.2
Digestive System		
Diarrhea	11.9	11.1
Dyspepsia	2.2	1.6
Nausea	26.4	13.1
Vomiting	18.1	9.3
Metabolic and Nutritional		
Amylase Increased	2.6	1.7
BUN Increased	2.5	0.5
Hypoproteinemia	5.1	3.3
SGOT Increased[c]	3.9	4.9
SGPT Increased[c]	4.6	5.2
Nervous System		
Dizziness	2.5	2.5
Skin and Appendages		
Rash	2.7	3.5

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] Vancomycin / Aztreonam, Imipenem / Cilastatin, Linezolid
[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 all Phase 3 and 4 studies that includes a comparator, death occurred in 4.0% (150/3788) of subjects receiving **TYGACIL** and 3% (110/3646) of subjects receiving comparator drugs. In a pooled analysis of these studies, the risk difference of all cause mortality was 0.9% (95% CI 0.1, 1.8) between tigecycline and comparator treated subjects. 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 subjects. No significant differences were observed between treatments by tigecycline and comparators by infection type (see Table 5). The cause of the imbalance has not been established. Generally, deaths were the result of worsening or complications of infection or underlying co-morbidities.

Table 5: Subjects with Outcome of Death by Infection Type

	-Tigecycline -		-Comparator -		Risk Difference*
Infection Type	n / N	%	n / N	%	% (95% CI)
cSSSI	12/834	1.4	6/813	0.7	0.7 (-0.5, 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[a]	41/336	12.2	42/345	12.2	0.0 (-5.1, 5.2)
VAP[a]	25/131	19.1	15/122	12.3	6.8 (-2.9, 16.2)
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 Unadjusted	150/3788	4.0	110/3646	3.0	0.9 (0.1, 1.8)
Overall Adjusted	150/3788	4.0	110/3646	3.0	0.6 (0.1, 1.2)**

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI = Complicated skin and skin structure infections; HAP = hospital-acquired pneumonia; VAP = ventilator-associated pneumonia; RP = resistant pathogens; DFI = diabetic foot infections.

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

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

The most common treatment-emergent adverse reactions in patients treated with tigecycline were nausea 29.9% (19.3% mild; 9.2% moderate; 1.4% severe) and vomiting 19.9% (12.1% mild; 6.8% moderate; 1.1% severe). In general, nausea or vomiting occurred early (days 1-2). Discontinuation from tigecycline was most frequently associated with nausea (1.6%) and vomiting (1.3%).

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 (1.1%) and vomiting (1.1%). For comparators, discontinuation was most frequently associated with nausea (0.5%).

The following treatment-emergent adverse reactions were reported infrequently (< 2%) in patients receiving **TYGACIL** in Phase 3 clinical studies:

Body as a Whole: injection site inflammation, injection site pain, injection site reaction, injection site edema, injection site phlebitis.

Cardiovascular System: thrombophlebitis.

Digestive System: anorexia, jaundice.

Metabolic / Nutritional System: bilirubinemia.

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

Skin and Appendages: pruritus.

For patients who received tigecycline, the following adverse reactions were reported:

Blood and lymphatic system disorders: Activated partial thromboplastin time prolonged (aPTT), prothrombin time prolonged (PT), international normalised ratio increased (INR), thrombocytopenia, hypofibrinogenaemia.

Immune system disorders: Anaphylactic reaction /anaphylactoid reactions.

Metabolism and nutrition disorders: Hypoproteinemia, hypoglycaemia, decreased appetite.

Nervous system disorders: Dizziness, headache.

Vascular disorders: Phlebitis, thrombophlebitis.

Respiratory, thoracic and mediastinal disorders: Pneumonia.

Gastrointestinal disorders: Nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, pancreatitis acute.

Hepatobiliary disorder: Aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased*, hyperbilirubinaemia, jaundice, cholestasis.

*AST and ALT abnormalities in tigecycline-treated patients were reported more frequently in the post-therapy period than in those in comparator-treated patients, which occurred more often on therapy.

Skin and subcutaneous tissue disorders: Pruritus, rash, severe skin reactions, including Stevens-Johnson Syndrome.

General disorders and administration site conditions: Impaired healing, injection site inflammation, injection site pain, injection site reaction, injection site oedema, injection site phlebitis.

Investigations: Amylase increased, blood urea increased (BUN).

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 cSSSI or for cIAI 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 dose of **TYGACIL** 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 **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**).

Safety and effectiveness in patients under 18 years of age have not been established. Therefore, use in patients under 18 years of age is not recommended (See **WARNINGS**). No dosage adjustment of **TYGACIL** is necessary based on age, gender, or race (See **CLINICAL PHARMACOLOGY, Special Populations, Geriatric Use, Gender, Race** and **PRECAUTIONS Geriatric Use**).

Preparation and Handling

The lyophilized powder 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. The vial should be gently swirled until the drug dissolves. 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 using two vials into a 100 mL IV bag. (Note: The vial contains a 6% overage. Thus, 5 mL of reconstituted solution is equivalent to 50 mg of the drug). 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 discolouration (e.g., green or black) prior to administration whenever solution and container permit. Once reconstituted, do not store **TYGACIL** above 25^{o}C for up to 24 hours (up to 6 hours in the vial and the remaining time in the IV bag). Alternatively, tigecycline mixed with 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP may be stored refrigerated at 2°C to 8°C (36°F 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.

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 **Compatibilities/Incompatibilities**).

Compatibilities/Incompatibilities
Compatible intravenous solutions include 0.9% Sodium Chloride Injection, USP, and 5% Dextrose Injection, USP, and Lactated Ringer's Injection, USP. When administered through a Y-site, **TYGACIL** is compatible with the following drugs or diluents when used with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP and administered simultaneously through the same line: amikacin, dobutamine, dopamine HCl, gentamicin, haloperidol, Lactated Ringer's, lidocaine HCl, metoclopramide, morphine, norepinephrine, piperacillin/tazobactam (EDTA formulation), potassium chloride, propofol, ranitidine HCl, theophylline and tobramycin.

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

ANIMAL TOXICOLOGY
Decreased erythrocytes, reticulocytes, leukocytes, and platelets, in association with bone marrow hypocellularity, have been seen with tigecycline at exposures of 8.1 times and 9.8 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.

Bolus intravenous administration of tigecycline has been associated with a histamine response in preclinical studies. These effects were observed at exposures of 14.3 and 2.8 times the human daily dose based on AUC in rats and dogs, respectively.

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

CLINICAL STUDIES
Complicated Skin and Skin Structure Infections (cSSSI)
TYGACIL was evaluated in adults for the treatment of cSSSI in two randomized, double-blind, active-controlled, multinational, multicenter studies. 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. Subjects 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) subjects. See Table 6.

Table 6. Clinical Cure Rates from Two Pivotal Studies in cSSSI after 5 to 14 Days of Therapy

	TYGACIL[a] n/N (%)	Vancomycin / Aztreonam[b] n/N (%)
CE	365 / 422 (86.5)	364 / 411 (88.6)
c-mITT	429 / 538 (79.7)	425 / 519 (81.9)

[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)

Clinical cure rates at TOC by pathogen in the ME subjects with cSSSI are presented in Table 7.

Table 7. Clinical Cure Rates by Infecting Pathogen in ME Subjects with cSSSI[a]

Pathogen	TYGACIL n/N (%)	Vancomycin / Aztreonam n/N (%)
Escherichia coli	29/ 36(80,6)	26/30 (86.7)
Enterobacter cloacae	10/12 (83.3)	15/15 (100)
Enterococcus faecalis (vancomycin-susceptible only)	15/21 (71.4)	19/24 (79.2)
Klebsiella pneumoniae	12/14 (85.7)	15/16 (93.8)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)[b]	124/137 (90.5)	113/120 (94.2)
Methicillin-resistant *Staphylococcus aureus* (MRSA)[b]	79/95 (83.2)	46/57 (80.7)
		10/12 (83.3)
CA-MRSA[c]	13/20 (65.0)	11 / 14 (78.6)
	8/8 (100)	9/10 (90.0)
Streptococcus agalactiae	17/21 (81.0)	24/27 (88.9)
Streptococcus anginosus grp.[d]	31/32 (96.9)	4/5 (80.0)
Streptococcus pyogenes	7/9 (77.8)	
Bacteroides fragilis		

[a] Two cSSSI pivotal studies and two Phase 3 Resistant Pathogen study
[b] Includes cases of concurrent bacteremia
[c] CA-MRSA = community acquired MRSA isolates that bear molecular and virulence markers commonly associated with community acquired MRSA including the SCC*mec* type IV element and the *pvl* gene
[d] Includes *Streptococcus anginosus, Streptococcus intermedius,* and *Streptococcus constellatus*

Complicated Intra-abdominal Infections (cIAI)

TYGACIL was evaluated in adults for the treatment of cIAI in two randomized, double-blind, active-controlled, multinational, multicenter studies. 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. Subjects with complicated diagnoses including appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of the 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 ME and the microbiologic modified intent-to-treat (m-mITT) subjects. See Table 8.

Table 8. Clinical Cure Rates from Two Pivotal Studies in cIAI after 5 to 14 Days of Therapy

	TYGACIL[a] n/N (%)	Imipenem / Cilastatin[b] n/N (%)
ME	441 / 512 (86.1)	442 / 513 (86.2)
m-mITT	506 / 631 (80.2)	514 / 631 (81.5)

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

Clinical cure rates at TOC by pathogen in the ME subjects are presented in Table 9.

Table 9. Clinical Cure Rates by Infecting Pathogen in ME Subjects with cIAI[a]

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

[a] Two cIAI pivotal studies and two Phase 3 Resistant Pathogen studies
[b] Includes ESBL producing isolates
[c] Includes cases of concurrent bacteremia
[d] Includes *Streptococcus anginosus, Streptococcus intermedius,* and *Streptococcus constellatus*

Methicillin-Resistant Staphylococcus aureus (MRSA) and Vancomycin-Resistant Enterococcus (VRE) spp.

TYGACIL was evaluated in adults for the treatment of various serious infections (cIAI, cSSSI, and other infections) due to VRE and MRSA in Study 307. Study 307 was a randomized, double-blind, active-controlled, multinational, multicenter study evaluating **TYGACIL** (100 mg IV initial dose followed by 50 mg every 12 hours) and vancomycin (1 g IV every 12 hours) for the treatment of infections due to MRSA and evaluating **TYGACIL** (100 mg IV initial dose followed by 50 mg every 12 hours) and linezolid

(600 mg IV every 12 hours) for the treatment of infections due to VRE for 7 to 28 days. Subjects with cIAI, cSSSI, and other infections were enrolled in this study. The primary efficacy endpoint was the clinical response at the TOC visit for the co-primary populations of the ME and the m-mITT patients. For clinical cure rates see Table 10 for MRSA and Table 11 for VRE.

Table 10. Clinical Cure Rates from Resistant Pathogen Study 307[a] for MRSA after 7 to 28 Days of Therapy

	TYGACIL[b] n/N (%)	Vancomycin[c] n/N (%)
Study 307		
ME	70/86 (81.4)	26/31 (83.9)
cIAI	13/14 (92.9)	4/4 (100.0)
cSSSi	51/59 (86.4)	20/23 (87.0)
m-mITT	75/100 (75.0)	27/33 (81.8)
cIAI	13/15 (86.7)	5/6 (83.3)
cSSSi	55/70 (78.6)	21/23 (87.0)

[a] Study included subjects with cIAI, cSSSI, and other infections.
[b] 100 mg initially, followed by 50 mg every 12 hours
[c] 1 g IV every 12 hours

Table 11. Clinical Cure Rates from Resistant Pathogen Study 307[a] for VRE after 7 to 28 Days of Therapy

	TYGACIL[b] n/N (%)	Linezolid[c] n/N (%)
Study 307		
ME	3/3 (100.0)	2/3 (66.7)
cIAI	1/1 (100.0)	0/1 (0.0)
cSSSI	1/1 (100.0)	2/2 (100.0)
m-mITT	3/8 (37.5)	2/3 (66.7)
cIAI	1/2 (50.0)	0/1 (0.0)
cSSSI	1/2 (50.0)	2/2 (100.0)

[a] Study included subjects with cIAI, cSSSI, and other infections.
[b] 100 mg initially, followed by 50 mg every 12 hours
[c] Linezolid (600 mg IV every 12 hours)

Resistant Gram-Negative Pathogens

TYGACIL was evaluated in adults for the treatment of various serious infections (cIAI, cSSSI, CAP, and other infections) due to resistant gram-negative pathogens in Study 309. Study 309 was an open-label, multinational, multicenter study evaluating **TYGACIL** (100 mg IV initial dose followed by 50 mg every 12 hours) for the treatment of infections due to resistant gram-negative pathogens for 7 to 28 days. Subjects with cIAI, cSSSI, CAP, and other infections were enrolled in this study. The primary efficacy endpoint was the clinical response at the TOC visit for the co-primary populations of the ME and the m-mITT subjects. See Table 12.

Table 12. Clinical Cure Rates from Resistant Pathogen Study 309[a] for Resistant Gram-negative Pathogens after 7 to 28 Days of Therapy

		TYGACIL[b] N/N (%)	TYGACIL[b] N/N (%)	TYGACIL[b] N/N (%)
Study 309	**All[c]**	***E. coli***	***Klebsiella pneumoniae***	***Enterobacter spp.***
ME	26/36 (72.2)	4/9 (44.4)	5/6 (83.3)	3/4 (75.0)
cIAI	2/2 (100.0)[d]	1/1 (100.0)[d]	1/1 (100.0)	-
cSSSI	20/24 (83.3)	3/5 (60.0)	3/3 (100.0)	3/3 (100.0)
CAP	0/1 (0.0)	-	-	0/1 (0.0)
m-mITT	40/75 (53.3)	5/10 (50.0)	9/13 (69.2)	8/15 (53.3)
cIAI	6/9 (66.7)[d]	2/2 (100.0)[d]	1/1 (100.0)	1/1 (100.0)[d]
cSSSI	27/38 (71.1)	3/5 (60.0)	6/7 (85.7)	7/8 (87.5)
CAP	0/1 (0.0)	-	-	0/1 (0.0)

[a] Study included subjects with cIAI, cSSSI, CAP and other infections.
[b] 100 mg initially, followed by 50 mg every 12 hours
[c] Includes other pathogens besides *E. coli*, *Klebsiella pneumoniae*, and *Enterobacter* spp.
[d] Excludes subjects with inadequate source control

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

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

Supplied 10 vials/box.

Storage
Prior to reconstitution, store **TYGACIL** below 30°C. Reconstituted solution must be immediately transferred and further diluted for IV infusion. Once reconstituted, do not store **TYGACIL** above 25°C for up to 24 hours (up to 6 hours in the vial and the remaining time in the IV bag). Alternatively, **TYGACIL** 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 IV bag.

Shelf life is 24 months from the date of manufacture.

HARUS DENGAN RESEP DOKTER

No Reg: DKI1334400244A1

Manufactured by:
Wyeth Lederle S.r.l.
Via Franco Gorgone Z.I.
95100 Catania (CT), Italy

Imported by:
PT. Pfizer Indonesia,
Jakarta, Indonesia