Tygacil®
(Tigecycline)

1. NAME OF THE MEDICINAL PRODUCT

TYGACIL (TIGECYCLINE) INJECTION 50 MG.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tigecycline for injection is supplied in single-dose, 5 ml, Type 1 glass vials containing 50 mg lyophilized powder for infusion.

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

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

Lyophilized orange cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tygacil is indicated for the treatment of the following infections (see sections 4.4 and 5.1):
- Complicated skin and soft tissue infections (cSSTI).
- Complicated intra-abdominal infections (cIAI).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Tigecycline is not indicated for the treatment of hospital-acquired or ventilator-associated pneumonia (see section 4.4).

4.2 Posology and method of administration

Posology
The recommended dose for adults is an initial dose of 100 mg followed by 50 mg every 12 hours for 5 to 14 days. The duration of therapy should be guided by the severity, site of the infection, and the patient's clinical response.

Hepatic insufficiency
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 25 mg every 12 hours following the 100 mg loading dose. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response (see sections 4.4 and 5.2).

Renal insufficiency
No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis (see section 5.2).

Elderly patients
In a pooled analysis of 3900 subjects who received tigecycline in Phase 3 and 4 clinical studies, 1026 were 65 years and over. Of these, 419 were 75 years and over. No unexpected overall differences in safety were observed between these subjects and younger subjects. No dosage adjustment is necessary in elderly patients (see section 5.2).

Pediatric patients
Tygacil is not recommended for use in children and adolescents below 18 years due to the lack of data on safety and efficacy (see sections 5.2 and 4.4).

Method of administration
Tygacil is administered only by intravenous infusion over 30 to 60 minutes (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. Patients hypersensitive to tetracycline class antibiotics may be hypersensitive to tigecycline.

4.4 Special warnings and precautions for use

An increase in all-cause mortality has been observed across Phase 3 and 4 clinical trials in tigecycline-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 in all-cause mortality should be considered when selecting among treatment options (see sections 4.4 and 4.8).

Anaphylactic reaction/anaphylactoid reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening.

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

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. Tigecycline may have adverse reactions similar to tetracycline class antibiotics. Such reactions may include photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic action, which have led to increased BUN, azotemia, acidosis, and hyperphosphatemia. Experience in the use of tigecycline for treatment of infections in patients with severe underlying diseases is limited.

Pancreatitis acute, which can be fatal, has occurred (frequency: uncommon) in association with tigecycline treatment (see section 4.8). 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 patients 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 section 4.8).

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 15/122 [12.3%]) 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.

In clinical trials in complicated skin and soft tissue infections, the most common type of infection in tigecycline-treated patients was cellulitis (59%), followed by major abscesses (27.5%). Patients with severe underlying disease, such as those that were immunocompromised, patients with decubitus ulcer infections, or patients that had infections requiring longer than 14 days of treatment (for example, necrotizing fasciitis), were not enrolled. Few patients with diabetic foot infections (5%) were enrolled. A limited number of patients were enrolled with co-morbid factors, such as diabetes (20%), peripheral vascular disease (7%), intravenous drug abuse (2%), and HIV-positive infection (1%). Limited experience is also available in treating patients with concurrent bacteremia (3%). Therefore, caution is advised when treating such patients.

In clinical trials in complicated intra-abdominal infections, the most common type of infection in tigecycline-treated patients was complicated appendicitis (51%), followed by other diagnoses less commonly reported, such as complicated cholecystitis (14%), intra-abdominal abscess (10%), perforation of intestine (10%) and gastric or duodenal ulcer perforation less than 24 hours (5%). Of these patients, 76% had associated diffuse peritonitis (surgically-apparent peritonitis). There were a limited number of patients with severe underlying disease, such as immunocompromised patients, patients with APACHE II scores >15 (4%), or with surgically apparent multiple intra-abdominal abscesses (10%). Limited experience is also available in treating patients with concurrent bacteremia (6%). Therefore, caution is advised when treating such patients.

Caution should be exercised when considering tigecycline monotherapy in patients with cIAI secondary to clinically apparent intestinal perforation. In Phase 3 and 4 cIAI studies (n=2775), 140/1382 tigecycline-treated subjects and 142/1393 comparator-treated subjects presented with intestinal perforations. Of these subjects, 8/140 subjects treated with tigecycline and 8/142 subjects treated with comparator developed sepsis/septic shock. The relationship of this outcome to treatment cannot be established (see section 4.8).

The effect of cholestasis in the pharmacokinetics of tigecycline has not been properly established. Biliary excretion accounts for approximately 50% of the total tigecycline excretion. Therefore, patients presenting with cholestasis should be closely monitored.

Prothrombin time or other suitable anticoagulation tests should be used to monitor patients if tigecycline is administered with anticoagulants (see section 4.5).

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 during or subsequent to the administration of any antibacterial agent.

The use of tigecycline may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

Results of studies in rats with tigecycline have shown bone discoloration. Tigecycline may be associated with permanent tooth discoloration in humans if used during tooth development.

Tygacil should not be used in children under 8 years of age because of teeth discoloration, and is not recommended in adolescents below 18 years due to the lack of data on safety and efficacy (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Concomitant administration of tigecycline (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single-dose) to healthy subjects resulted in a decrease in clearance of R-warfarin and S-warfarin by 40% and 23%, and an increase in AUC by 68% and 29%, respectively. The mechanism of this interaction is still not elucidated. Available data does not suggest that this interaction may result in significant INR changes. However, since tigecycline may prolong both prothrombin time (PT) and activated partial thromboplastin time (aPTT), the relevant coagulation tests should be closely monitored when tigecycline is co-administered with anticoagulants (see section 4.4). Warfarin did not affect the pharmacokinetic profile of tigecycline.

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, tigecycline is not expected to alter the metabolism of drugs metabolized by these enzymes. Tigecycline is not extensively metabolized. Therefore, clearance of tigecycline is not expected to be affected by active substances that inhibit or induce the activity of the CYP450 isoforms. *In vitro*, tigecycline is not competitive inhibitor of CYP450 enzymes (see section 5.2). However, mechanism-based inhibition has not been evaluated, and cannot be excluded (see warfarin interaction above).

Tigecycline in recommended dosage (100 mg followed by 50 mg every 12 hours) did not affect the rate or extent of absorption, or clearance of digoxin (0.5 mg followed by 0.25 mg daily) when administered in healthy adults in a drug interaction study. Tigecycline slightly decreased the C_{max} of digoxin by 13%, this small change in C_{max} did not affect the

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

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

Concurrent use of antibiotics with oral contraceptives may render oral contraceptives less effective.

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.

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. Co-administration of P-gp inhibitors (e.g., ketoconazole or cyclosporine) or P-gp inducers (e.g., rifampicin) could affect the pharmacokinetics of tigecycline.

There are no reported drug-laboratory test interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy
Tigecycline may cause fetal harm when administered to a pregnant woman. There are no adequate data from the use of tigecycline in pregnant women. Results from animal studies have shown tigecycline may cause fetal harm when administered during pregnancy.

The potential risk for humans is unknown. As it is known for tetracycline class antibiotics, tigecycline may also induce permanent dental defects (discoloration and enamel defects) and a delay in ossification processes in fetuses, exposed *in utero* during the last half of gestation, and in children under eight years of age due to the enrichment in tissues with a high calcium turnover and formation of calcium chelate complexes (see section 4.4). Tigecycline should not be used during pregnancy unless clearly necessary.

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 section 5.3).

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

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

Lactation
It is not known whether this medicinal product is excreted in human milk. Available data in animals have shown excretion of tigecycline/metabolites in milk (see section 5.3). Because a potential risk to the breast-feeding infant cannot be ruled out, when treating with tigecycline, caution should be exercised and interruption of breast-feeding should be considered.

Fertility
The effects of tigecycline on fertility in humans have not been studied. Non-clinical studies conducted with tigecycline in rats do not indicate harmful effects with respect to fertility or reproductive performance (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of tigecycline on the ability to drive and use machines have been performed. Dizziness may occur and this may have an effect on driving and use of machines (see section 4.8).

4.8 Undesirable effects

The total number of patients treated with tigecycline in Phase 3 clinical studies was 1415. Adverse reactions were reported in approximately 41% of patients treated with tigecycline. Treatment was discontinued due to adverse reactions in 5% of patients.

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 clinical trials, the following adverse reactions were reported:

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Frequency not known (cannot be estimated from the available data).

Infections and infestations:
Common: Abscess, infections
Uncommon: Sepsis/septic shock

In Phase 3 clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with tigecycline (6.7%) vs. comparators (4.6%). Significant

differences in sepsis/septic shock with tigecycline (1.5%) vs. comparators (0.5%) were observed.

Blood and the lymphatic system disorders:
Common: Activated partial thromboplastin time prolonged (aPTT), prothrombin time prolonged (PT), thrombocytopenia
Uncommon: International Normalized Ratio increased (INR)
Rare: Hypofibrinogenemia

Immune system disorders:
Frequency not known: Anaphylactic reaction/anaphylactoid reaction (see sections 4.3 and 4.4)

Metabolism and nutrition disorders:
Common: Hypoproteinemia, hypoglycemia, decreased appetite

Nervous system disorders:
Common: Dizziness, headache

Vascular disorders:
Common: Phlebitis
Uncommon: Thrombophlebitis

Respiratory, thoracic and mediastinal disorders:
Common: Pneumonia

Gastrointestinal disorders:
Very common: Nausea, vomiting, diarrhea
Common: Abdominal pain, dyspepsia
Uncommon: Pancreatitis acute (see section 4.4)

Hepato-biliary disorders:
Common: Aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, hyperbilirubinemia
Uncommon: Jaundice
Frequency not known: Cholestasis

AST and ALT abnormalities in Tygacil-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:
Common: Pruritus, rash
Frequency not known: Severe skin reactions, including Stevens-Johnson syndrome

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

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

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. In a pooled analysis of these trials, 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 random effects model by trial weight, an adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1,1.2) between tigecycline-treated and comparator-treated subjects. No significant differences were observed between tigecycline and comparator by infection type (see Table 1). The cause of the imbalance has not been established. Generally, deaths were the result of worsening infection or complications of infection or underlying co-morbidities.

Table 1. Subjects with Outcome of Death by Infection Type

	Tigecycline		Comparator		Risk Difference*
Infection Type	**n/N**	**%**	**n/N**	**%**	**% (95% CI)**
cSSTI	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; cSSTI = Complicated skin and soft tissue 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 effect 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 (cSSTI), 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).

4.9 Overdose

No specific information is available on the treatment of overdose. Intravenous administration of tigecycline at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. In single-dose IV toxicity studies conducted with tigecycline in mice, the estimated median lethal dose (LD50) was 124 mg/kg in males and 98 mg/kg in females. In rats, the estimated LD50 was 106 mg/kg for both sexes. Tigecycline is not removed in significant quantities by hemodialysis.

4.10 Abuse and dependence

Drug abuse and dependence have not been demonstrated and are unlikely.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infective, Glycylcycline antibacterial, ATC code: J01C AA12.

Mode of action
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 is unique to tigecycline.

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*.

Mechanism of resistance
Tigecycline is able to overcome the two major tetracycline resistance mechanisms, ribosomal protection and efflux. However, in recent studies, resistance to tigecycline has been detected in *Enterobacterales* and other organisms, determined by an efflux pump mechanism and by mutations in a ribosomal protein. Tigecycline has demonstrated *in vitro* and *in vivo* activity against a broad spectrum of bacterial pathogens. However, it is vulnerable to chromosomally-encoded multidrug efflux pumps of *Proteeae* (see below) and *Pseudomonas aeruginosa* (MexXY-OprM efflux system). There is no target-based cross-resistance between tigecycline and most classes of antibiotics.

Pathogens of the family *Proteeae* (*Proteus* spp., *Providencia* spp., and *Morganella* spp.) are generally less susceptible to tigecycline than other members of the *Enterobacteriaceae*. In addition, some acquired resistance has been detected in *Klebsiella pneumoniae, Enterobacter aerogenes*, and *Enterobacter cloacae.* Decreased susceptibility in both groups has been attributed to the overexpression of the non-specific AcrAB multi-drug efflux pump. Decreased susceptibility in *Acinetobacter baumannii* has also been reported.

***In Vitro* Susceptibility of Bacteria to Tigecycline**
For broth dilution tests for aerobic organisms, MICs must be determined using testing medium that is fresh (<12 hours old). The disk diffusion procedure utilizes disks impregnated with 15 µg of tigecycline.

EUCAST reference information
Minimum inhibitory concentration (MIC) and disk inhibition zone breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows [The European Committee on Antimicrobial Susceptibility Testing]. Breakpoint tables for interpretation of MICs and zone diameters:

Table 2. EUCAST Breakpoints		
Pathogen	**MIC (mg/L)**	**Inhibition zone diameter (mm)**
	≤S (Susceptible) / >R (Resistant)	**≥S (Susceptible) / <R (Resistant)**
Enterobacterales (formerly *Enterobacteriaceae*): *Escherichia coli* and *Citrobacter koseri*: (†)	≤0.5 / >0.5	≥18 / <18(*)
Staphylococcus spp.	≤0.5 / >0.5	≥19 / <19
Enterococcus faecalis	≤0.25 / >0.25	≥20 / <20
Enterococcus faecium	≤0.25 / >0.25	≥22 / <22
Streptococcus groups A, B, C and G	≤0.125 / >0.125	≥19 / <19
PK/PD (non-species related)		
≤0.5 / >0.5		-

(†)For other *Enterobacterales*, the activity of tigecycline varies from insufficient in *Proteus* spp., *Morganella morganii* and *Providencia* spp. to variable in other species.
(*)Zone diameter breakpoints validated for *E. coli* only. For *C. koseri* use MIC method.

For anaerobic bacteria there is clinical evidence of efficacy in polymicrobial intra-abdominal infections, but no correlation between MIC values, PK/PD data and clinical outcome. Therefore, no breakpoint for susceptibility is given.

Quality control ranges for EUCAST susceptibility testing are in the following table.

Table 3. Acceptable Quality Control Ranges for Susceptibility Testing (EUCAST)		
Organism	**MIC range (mg/L)**	**Inhibition zone diameter range (mm)**
Escherichia coli ATCC 25922	0.03-0.25	20-27
Staphylococcus aureus ATCC 29213	0.03-0.25	19-25
Enterococcus faecalis ATCC 29212	0.03-0.125	20-26
Streptococcus pneumoniae ATCC 49619	0.016-0.125	24-30

ATCC = American Type Culture Collection.

PK/PD relationship
Limited animal data indicates that AUC/MIC is the pharmacodynamic index best related to outcome. Human pharmacodynamic studies indicate a relationship between AUC/MIC and clinical as well microbiological efficacy.

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

The information below provides only approximate guidance on the probability as to whether the microorganism will be susceptible to tigecycline or not.

Pathogen
Commonly susceptible species
Gram-positive Aerobes *Enterococcus* spp.† *Staphylococcus aureus** (including methicillin resistant isolates) *Staphylococcus epidermidis* *Staphylococcus haemolyticus* *Streptococcus agalactiae** *Streptococcus pyogenes** Viridans group streptococci† Gram-negative Aerobes *Citrobacter freundii** *Citrobacter koseri* *Escherichia coli** Anaerobes *Clostridium perfringens** *Peptostreptococcus* spp.† *Prevotella* spp.
Species for which acquired resistance may be a problem
Gram-negative Aerobes *Acinetobacter baumannii* *Enterobacter cloacae** *Klebsiella aerogenes* *Klebsiella oxytoca** *Klebsiella pneumoniae** *Stenotrophomonas maltophilia* Anaerobes *Bacteroides fragilis* group†
Inherently resistant organisms
Gram-negative Aerobes *Morganella morganii* *Providencia* spp. *Proteus* spp. *Serratia marcescens* *Pseudomonas aeruginosa*

* Denotes species against which it is considered that activity has been satisfactorily demonstrated in clinical studies.

† Activity in clinical studies has been demonstrated for vancomycin-susceptible *Enterococcus faecalis*; among viridans streptococci for the *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius* and *S. constellatus*); among *Peptostreptococcus* spp. for *P. micros*; among *Bacteroides* spp. for *B. fragilis*, *B. thetaiotaomicron*, *B. uniformis* and *B. vulgatus*.

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.

5.2 Pharmacokinetic properties

The mean pharmacokinetic parameters of tigecycline for the recommended dosage regimen after single and multiple intravenous doses are summarized in Table 4.

Table 4. Mean (CV %) Pharmacokinetic Parameters of Tigecycline

	Single Dose	**Multiple Dose[c]**
	100 mg	**50 mg q12h**
C_{max} (µg/ml)[a]	1.45 (22%)	0.87 (27%)
C_{max} (µg/ml)[b]	0.90 (30%)	0.63 (15%)
AUC (µg·h/ml)	5.19 (36%)	-
AUC_{0-24h} (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] 30-minute infusion.
[b] 60-minute infusion.
[c] 100 mg initially, followed by 50 mg every 12 hours.

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, salivary glands, thyroid gland, spleen, and kidney. In humans, the steady-state volume of distribution of tigecycline averaged 500 to 700 L (7 to 9 L/kg), indicating that tigecycline is extensively distributed beyond the plasma volume and concentrates into tissues.

No data are available on whether tigecycline can cross the blood-brain barrier in humans.

In clinical pharmacology studies using the therapeutic dosage regimen of 100 mg followed by 50 mg q12h, serum tigecycline steady-state C_{max} was 866±233 ng/ml for 30-minute infusions and 634±97 ng/ml for 60-minute infusions. The steady-state AUC_{0-12h} was 2349±850 ng•h/ml.

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_{0-12h} (134 µg·h/ml) in alveolar cells was approximately 77.5-fold higher than the AUC_{0-12h} in the serum of these subjects, and the AUC_{0-12h} (2.28 µg·h/ml) in epithelial lining fluid was approximately 32% higher than the AUC_{0-12h} in serum. In a skin blister study, the AUC_{0-12h} (1.61 µg·h/ml) of tigecycline in skin blister fluid was approximately 26% lower than the AUC_{0-12h} 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
On average, it is estimated that less than 20% of tigecycline is metabolized before excretion. In healthy male volunteers, following the administration of ^{14}C-tigecycline, unchanged tigecycline was the primary ^{14}C-labelled 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.

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, tigecycline is not expected to alter the metabolism of drugs metabolized by these enzymes.

In vitro studies with tigecycline using human liver microsomes, liver slices, and hepatocytes led to the formation of only trace amounts of metabolites.

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

The total clearance of tigecycline is 24 L/h after intravenous infusion. Renal clearance is approximately 13% of total clearance. Tigecycline shows a poly-exponential elimination from serum with a mean terminal elimination half-life after multiple doses of 42 hours although high inter-individual variability exists.

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

Hepatic Insufficiency
In a study comparing 10 subjects with mild hepatic impairment (Child Pugh A), 10 subjects with moderate hepatic impairment (Child Pugh B), and five 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 55% and the half-life of tigecycline was prolonged by 23% and 43% in subjects with moderate or severe hepatic impairment (Child Pugh B and C), respectively (see section 4.2).

Renal Insufficiency
A single-dose study compared 6 subjects with severe renal impairment (creatinine clearance Cl_{Cr} ≤30 ml/min), 4 end stage renal disease subjects receiving tigecycline 2 hours before hemodialysis, 4 end stage renal disease subjects receiving tigecycline 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. In severe renal impairment, AUC was 30% higher than in subjects with normal renal function (see section 4.2).

Elderly Patients
No overall differences in pharmacokinetics were observed between healthy elderly subjects (n=15, age 65-75; n=13, age >75) and younger subjects (n=18) receiving a single, 100 mg dose of tigecycline (see section 4.2).

Pediatric Patients
The pharmacokinetics of tigecycline in patients less than 18 years of age has not been established (see section 4.2).

Gender
In a pooled analysis of 38 women and 298 men participating in clinical pharmacology studies, there were no clinically relevant differences in the clearance of tigecycline between men and women. AUC was estimated to be 20% higher in females than in males. 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 (22.8±8.8 L/h), Black subjects (23.0±7.8 L/h), Hispanic subjects (24.3±6.5 L/h), White subjects (22.1±8.9 L/h), and "other" subjects (25.0±4.8 L/h). Therefore, no dosage adjustment is necessary based on race. There were no differences in the clearance of tigecycline based on race.

Weight
Clearance, weight-normalized clearance, and AUC were not appreciably different among patients with different body weights, including those weighing ≥125 kg. AUC was 24% lower in patients weighing ≥125 kg. No data is available for patients weighing 140 kg and more.

5.3 Preclinical safety data

Carcinogenicity
Lifetime studies in animals to evaluate the carcinogenic potential of tigecycline have not been performed, but short-term genotoxicity studies of tigecycline were negative.

Mutagenicity
No mutagenic or clastogenic potential was found in a battery of tests, including an *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.

Reproduction toxicity
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 estrus 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.

Other
In repeated dose toxicity studies in rats and dogs, lymphoid depletion/atrophy of lymph nodes, spleen and thymus, decreased erythrocytes, reticulocytes, leukocytes, and platelets, in association with bone marrow hypocellularity, and adverse renal and gastrointestinal effects have been seen with tigecycline at exposures of 8.1 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.

Bone discoloring was observed in rats, which was not reversible after two weeks of dosing.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hydrochloric acid, sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

The following active substances should not be administered simultaneously through the same Y-site as Tygacil: Amphotericin B, amphotericin B lipid complex, diazepam, esomeprazole and omeprazole.

Tygacil must not be mixed with other medicinal products for which compatibility data are not available (see section 6.6).

6.3 Storage conditions

Once reconstituted and diluted in the bag or other suitable infusion container (e.g., glass bottle), tigecycline should be used immediately.

6.4 Special precautions for storage

Do not store above 30°C.

For storage conditions of the reconstituted product, see section 6.3.

6.5 Nature and contents of container

5 ml Type 1 clear glass vials fitted with grey butyl rubber stoppers and snap-off aluminium crimp seals.

Tygacil is distributed in a ten-vial tray pack.

6.6 Special precautions for disposal

The lyophilized powder should be reconstituted with 5.3 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection to achieve a concentration of 10 mg/ml of tigecycline. The vial should be gently swirled until the medicinal product is dissolved. Thereafter, 5 ml of the reconstituted solution should be immediately withdrawn from the vial and added to a 100 ml intravenous bag for infusion or other suitable infusion container (e.g., glass bottle).

For a 100 mg dose, reconstitute using two vials into a 100 ml intravenous bag or other suitable infusion container (e.g., glass bottle). Note: The vial contains a 6% overage. Thus, 5 ml of reconstituted solution is equivalent to 50 mg of the active substance. The reconstituted solution should be yellow to orange in color; if not, the solution should be discarded. Parenteral products should be inspected visually for particulate matter and discoloration (e.g., green or black) prior to administration.

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 active substances, the line should be flushed before and after infusion of Tygacil with either sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection. Injection should be made with an infusion solution compatible with tigecycline and any other medicinal product(s) via this common line (see section 6.2).

Compatible intravenous solutions include: sodium chloride 9 mg/ml (0.9%) solution for injection and dextrose 50 mg/ml (5%) solution for injection.

When administered through a Y-site, compatibility of Tygacil diluted in sodium chloride 0.9% for injection is demonstrated with the following medicinal products or diluents: amikacin, dobutamine, dopamine HCl, gentamicin, haloperidol, lidocaine HCl, potassium chloride, ranitidine HCl, Lactated Ringer's, metoclopramide, morphine, norepinephrine, piperacillin/tazobactam (EDTA formulation), propofol, tobramycin and theophylline.

This medicinal product is for single use only; any unused solution should be discarded.

7. PRODUCT OWNER

Pfizer Inc
New York,
United States

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