NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Tygacil® 50 mg Powder for Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL glass vial of Tygacil contains 50 mg tigecycline lyophilised powder for intravenous infusion.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Powder for intravenous infusion.

Orange cake or powder.

The reconstituted solution is yellow to orange, essentially free of particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tygacil is indicated for the treatment of the following infections in adults:

- Complicated skin and skin structure infections, including those with methicillin-resistant Staphylococcus aureus (MRSA), where there is suspected or proven resistance to, intolerance of, or there are co-morbidities preventing the use of, other available agents.
- Complicated intra-abdominal infections, where there is suspected or proven resistance to, intolerance of, or there are co-morbidities preventing the use of, other available agents.

4.2 Dose and Method of Administration

Adult

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

The recommended duration of treatment with tigecycline for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days. The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress.

Children and Adolescent

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.

Elderly

No dosage adjustment is necessary in elderly patients.

Hepatic Impairment

No dosage adjustment is necessary in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). Based on the pharmacokinetic profile of tigecycline in patients with severe hepatic impairment (Child Pugh C), the dose of tigecycline should be altered to 100 mg followed by 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response (see Section 5.2, Special Populations, Hepatic Impairment).

Renal Impairment

No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing haemodialysis (see Section 5.2, Special Populations, Renal Impairment).

Race and Gender

No dosage adjustment is necessary based on race or gender (see Section 5.2, Special Populations, Race, Gender).

Mode of Administration

Tygacil is administered only by intravenous infusion over approximately 30 to 60 minutes (see Section 6.6). For instructions on reconstitution & dilution of the medicinal product before administration, see Section 6.6.

4.3 Contraindications

Tygacil is contraindicated for use in patients who have known hypersensitivity to tigecycline or any of the excipients listed in Section 6.1 List of excipients.

4.4 Special Warnings and Precautions for Use

All-cause Mortality

An increase in all-cause mortality has been observed across Phase 3 and 4 clinical trials in tigecycline-treated patients versus comparator-treated patients. In a pooled analysis of all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of patients receiving tigecycline and 3.0% (110/3646) of patients receiving comparator drugs 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 patients. The cause of this increase has not been established. This increase in all-cause mortality should be considered when selecting among treatment options (see Section 4.8).

The increased risk in all-cause mortality was greater in patients treated for hospital-acquired pneumonia, especially ventilator-associated pneumonia, but was also seen at a lower rate in patients with complicated skin and skin structure infections, complicated intra-abdominal infections and diabetic foot infections. No increased risk in all-cause mortality was observed in patients with community-acquired pneumonia (see Table 2). Tygacil is not approved for the treatment of hospital-acquired pneumonia (including ventilator-associated pneumonia), community-acquired pneumonia or diabetic foot infections.

Anaphylactic Reaction/Anaphylactoid Reaction

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

Hypersensitivity to Tetracycline-class Antibiotics

Tygacil is a tetracycline class antibiotic in the glycylcycline subcategory and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic action (which has led to increased plasma urea, azotaemia, acidosis, and hyperphosphataemia). Therefore, tigecycline should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics.

Pancreatitis Acute

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 cases suspected of having developed pancreatitis.

Monitoring of Blood Coagulation Parameters

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).

Patients with Hospital-acquired Pneumonia

The safety and efficacy of tigecycline in patients with hospital-acquired pneumonia have not been established. In a study of patients with hospital-acquired pneumonia, patients were randomised to receive tigecycline (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. The sub-group of patients with ventilator-associated pneumonia who received tigecycline had lower cure rates (47.9% versus 70.1% for the clinically evaluable population) and greater mortality (25/131 [19.1%] versus 15/122 [12.3%]) than the comparator. Of those patients with ventilator-associated pneumonia and bacteraemia at baseline, those who received tigecycline had greater mortality (9/18 [50.0%] versus 1/13 [7.7%]) than the comparator.

Tooth Discolouration

Tigecycline may be associated with permanent tooth discolouration in the teeth in humans during tooth development

Pseudomembranous Colitis

Pseudomembranous colitis has been reported with nearly all antibiotics. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis e.g., opiates and diphenoxylate with atropine may prolong and/or worsen the condition and should not be used.

Superinfection

As with other antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

Development of Drug-resistant Bacteria

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

Patients with Complicated Intra-abdominal Infections (cIAI)

Caution should be exercised when considering tigecycline monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation (see Section 4.8). In Phase 3 cIAI studies (n=1642), 6 patients treated with tigecycline and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with tigecycline had higher APACHE II scores (median = 13) vs the 2 patients treated with imipenem/cilastatin (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.

Histamine Response

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.

Impaired Hepatic Function

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

Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response (see Section 5.1).

4.5 Interaction with Other Medicines and Other Forms of Interaction

Digoxin

Tigecycline (100 mg followed by 50 mg every 12 hours) and digoxin (0.5 mg followed by 0.25 mg every 24 hours) were co-administered to healthy subjects in a drug interaction study. Tigecycline slightly decreased the C_{max} of digoxin by 13%, but did not affect the AUC or clearance of digoxin. This small change in C_{max} did not affect the steady-state pharmacodynamic effects of digoxin as measured by changes in ECG intervals. In addition, digoxin did not affect the pharmacokinetic profile of tigecycline. Therefore, no dosage adjustment is necessary when tigecycline is administered with digoxin.

Warfarin

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

Cytochrome P450 Isoforms

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 metabolised by these enzymes. In addition, because tigecycline is not extensively metabolised, clearance of tigecycline is not expected to be affected by drugs that inhibit or induce the activity of these CYP450 isoforms.

P-glycoprotein Inhibitors

As tigecycline is a substrate of P-glycoprotein (P-gp), co-administration of P-gp inhibitors (e.g., ketoconazole or ciclosporin) or P-gp inducers (e.g., rifampicin) could affect the pharmacokinetics of tigecycline.

Oral Contraceptives

No clinical studies have been conducted on the interaction between tigecycline and oral contraceptives, however, concurrent use of antibiotics with oral contraceptives may render oral contraceptives less effective. It is recommended that an additional barrier method of contraception should be used when using Tygacil.

Calcineurin Inhibitors

Concomitant use of tigecycline and calcineurin inhibitors such as tacrolimus or ciclosporin 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.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Tygacil may cause fetal harm when administered to a pregnant woman.

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. Tygacil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Tygacil has not been studied for use during labour and delivery.

Breast-feeding

It is not known whether this drug is excreted in human milk. Available data in animals have shown excretion of tigecycline/metabolites in milk (see Section 5.3). Because many drugs are excreted in human milk, caution should be exercised when Tygacil is administered to a nursing woman.

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 Section 5.3).

4.7 Effects on Ability to Drive and Use Machinery

Tygacil can cause dizziness (see Section 4.8), which may impair the ability to drive and/or operate machinery.

4.8 Undesirable Effects

Clinical Trials

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

Phase 3 clinical studies enrolled 1415 patients treated with tigecycline. Adverse reactions (as judged by investigators) to be related to the medicinal product were reported in approximately 40.6% of patients treated with tigecycline.

Table 1: Incidence (%) of Treatment Emergent Adverse Events Through Test of Cure

Body System	**Tygacil[a]**	**Comparators[b]**
Adverse Events	**(N=1415)**	**(N=1382)**
Infections and Infestations		
Abscess	3.2	2.6
Infection	8.3	5.4
Blood and Lymphatic System Disorders		
Anaemia	4.2	4.8
Leukocytosis	3.7	2.5
Thrombocythaemia	6.1	6.2
Metabolic and Nutritional Disorders		
Hyperglycaemia	1.8	2.9
Hypokalaemia	2.1	2.9
Hypoproteinaemia	4.5	3.0

Body System	Tygacil[a]	Comparators[b]
Nervous System Disorders		
Dizziness	3.5	2.7
Insomnia	2.3	3.3
Headache	5.9	6.5
Vascular Disorders		
Hypertension	4.9	5.6
Hypotension	2.3	1.7
Phlebitis	1.8	3.8
Respiratory, Thoracic and Mediastinal Disorders		
Cough increased	3.7	3.8
Dyspnoea	2.9	2.7
Pulmonary physical finding	1.9	2.2
Gastrointestinal Disorders		
Abdominal pain	6.8	5.7
Constipation	2.8	4.1
Diarrhoea	12.7	10.8
Dyspepsia	2.9	1.6
Nausea	29.5	15.8
Vomiting	19.7	10.8
Hepatobiliary Disorders		
Hyperbilirubinaemia	2.3	0.9
Skin and Subcutaneous Tissue Disorders		
Pruritus	2.6	4.1
Rash	2.4	4.1
Hyperhidrosis	2.3	1.6
Musculoskeletal and Connective Tissue Disorders		
Back pain	1.2	2.3
General Disorders and Administration Site Conditions		
Asthenia	2.5	1.7
Pyrexia	7.1	9.8
Pain	3.7	2.9
Impaired healing	3.5	2.6
Peripheral oedema	3.3	3.3
Local reaction to procedure	9.0	9.1
Investigations		
Alkaline phosphatase increased	3.5	2.6
Amylase increased	3.1	1.4
Blood urea increased	2.1	0.2
Lactic dehydrogenase increased	4.0	3.5
AST increased[c]	4.3	4.4
ALT increased[c]	5.6	4.7

[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 Phase 3 clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with Tygacil (6.7%) vs. comparator (4.6%). Significant differences in sepsis/septic shock with Tygacil (1.5%) vs. comparators (0.5%) were observed. Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established (see Section 4.4). Other events included non-

significant differences in abscess (1.8% vs. 1.6%) and infections, including wound infections (1.7% vs. 1.1%) for Tygacil vs. comparator respectively.

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.

The most common treatment-emergent adverse reactions in patients treated with tigecycline were nausea 26.4% (16.9% mild; 8.1% moderate; 1.3% severe) and vomiting 18.1% (11.0% mild; 6.1% moderate; 1.0% severe). In general, nausea or vomiting occurred early (days 1-2).

Discontinuation from tigecycline was most frequently associated with nausea (1.1%) and vomiting (1.1%).

Treatment was discontinued due to adverse reactions in 5.0% of patients. Discontinuation from tigecycline was most frequently associated with nausea (1.3%) and vomiting (1.0%).

In a pooled analysis of 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of patients receiving Tygacil and 3.0% (110/3646) of patients 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 patients. In a pooled analysis of these trials, based on a random effects model by trial weight, an adjusted risk difference of all-cause mortality was 0.6% (95 % CI 0.1, 1.2) between tigecycline and comparator-treated patients. No significant differences were observed between treatments by infection type (see Table 2). 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 2: Patients 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 patients 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 patients with MRSA or Vancomycin-Resistant Enterococcus (VRE)), and 319 (DFI with and without osteomyelitis).

Post-marketing Experience

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

Post-marketing adverse reactions not previously listed in the product information or determined to have a greater frequency in post-marketing use include:

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

System Organ Class	*Adverse Reaction*
Blood and Lymphatic System Disorders	
Common	Activated partial thromboplastin time prolonged (aPTT), prothrombin time prolonged (PT), thrombocytopenia
Uncommon	International normalised ratio increased (INR)
Rare	Hypofibrinogenaemia
Immune System Disorders	
Frequency not known	Anaphylactic reaction/anaphylactoid reaction
Metabolism and Nutrition Disorders	
Common	Hypoglycaemia, decreased appetite
Vascular Disorders	
Uncommon	Thrombophlebitis
Respiratory, Thoracic and Mediastinal Disorders	
Common	Pneumonia
Gastrointestinal Disorders	
Uncommon	Pancreatitis acute
Hepatobiliary Disorders	
Common	Aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased
Uncommon	Jaundice
Frequency not known	Cholestasis
Skin and Subcutaneous Tissue Disorders*	
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

* Tigecycline is structurally similar to tetracycline-class antibacterial drugs and may have similar adverse effects. Such effects may include: Fixed drug eruption.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

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

Contact the National Poisons Centre on 0800 764 766 for advice on the management of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Anti-infective
Glycylcycline antibacterial
ATC code: J01AA12

Mechanism of Action

Tigecycline, a tetracycline class antibiotic in the glycylcycline subcategory, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. Tigecycline carries a glycylamido moiety attached to the 9-position of minocycline. The substitution pattern is not present in any naturally occurring or semisynthetic tetracycline and imparts certain microbiologic properties to tigecycline. In addition, 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.

There has currently been no cross-resistance observed between tigecycline and other antibiotics. *In vitro* studies have not demonstrated antagonism between tigecycline and other commonly used antibiotics. In general, tigecycline is considered bacteriostatic.

Tigecycline is not affected by resistance mechanisms such as β-lactamases (including extended spectrum β-lactamases), target site modifications, macrolide efflux pumps or enzyme target changes (e.g., gyrase/topoisomerase).

***In Vitro* Susceptibility of Bacteria to Tigecycline**

For broth dilution tests for aerobic organisms, minimum inhibitory concentrations (MIC) must be determined using testing medium that is fresh (<12 hours old). The disk diffusion procedure utilises disks impregnated with 15 µg of tigecycline.

European Committee on Antimicrobial Susceptibility Testing (EUCAST) Reference Information:

Minimum inhibitory concentration (MIC) and disk inhibition zone breakpoints established by EUCAST are as follows.

Breakpoint tables for interpretation of MICs and zone diameters:

Table 3. 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 4. 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 as 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.

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.† (including vancomycin resistant isolates)
- *Listeria monocytogenes*
- *Staphylococcus aureus* (*including methicillin-resistant isolates*)*
- *Staphylococcus epidermidis* (including methicillin resistant isolates)
- *Staphylococcus haemolyticus*
- *Streptococcus agalactiae**
- *Streptococcus pyogenes**
- *Streptococcus pneumoniae*†
- Viridans group streptococci†

Gram-negative aerobes

- *Aeromonas hydrophila*
- *Citrobacter freundii**
- *Citrobacter koseri*
- *Escherichia coli**
- *Haemophilus influenzae**
- *Legionella pneumophila**
- *Moraxella catarrhalis**
- *Neisseria gonorrhoeae*
- *Neisseria meningitidis*
- *Pasteurella multocida*

Anaerobes

- *Clostridioides difficile*
- *Clostridium perfringens**
- *Peptostreptococcus* spp.†
- *Porphyromonas* spp.
- *Prevotella* spp.

Other organisms

- *Chlamydia pneumoniae*
- *Mycobacterium abscessus*
- *Mycobacterium chelonae*
- *Mycobacterium fortuitum*
- *Mycoplasma pneumoniae*

Species for Which Acquired Resistance May be a Problem

Gram-negative aerobes

- *Acinetobacter baumannii*
- *Enterobacter cloacae**
- *Klebsiella aerogenes*
- *Klebsiella oxytoca**
- *Klebsiella pneumoniae**

- *Morganella morganii*
- *Salmonella* spp.
- *Serratia marcescens*
- *Shigella* spp.
- *Stenotrophomonas maltophilia*

Anaerobes

- *Bacteroides fragilis* group†
- *Parabacteroides distasonis*

Inherently Resistant Organisms

Gram-negative aerobes

- *Providencia* spp.
- *Proteus* spp.
- *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*; penicillin-susceptible pneumococci; 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, B. ovatus* and *B. vulgatus*.

Clinical Efficacy and Safety

Complicated Skin and Skin Structure Infections

Tigecycline was evaluated in adults for the treatment of complicated skin and skin structure infections (cSSSI) in two randomised, double-blind, active-controlled, multinational, multicenter studies. These studies compared tigecycline (100 mg IV initial dose followed by 50 mg every 12 hours) with vancomycin (1 g IV every 12 hours)/aztreonam (2 g IV every 12 hours) for 5 to 14 days. Patients with complicated deep soft-tissue infections including wound infections and cellulitis (≥10 cm, requiring surgery/drainage or with complicated, underlying disease), major abscesses, infected ulcers, and burns were enrolled in the studies. Patients with chronically infected ulcers, peripheral vascular disease requiring amputation, necrotising infections and contiguous osteomyelitis were not included in these studies. The primary efficacy endpoint was the clinical response at the test of cure (TOC) visit in the co-primary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) patients. See Table 5 below.

Table 5: Clinical Cure Rates from Two Pivotal Studies in Complicated Skin and Skin Structure Infection After 5 to 14 Days of Therapy

	Tigecycline[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 test of cure (TOC) by pathogen in microbiologically evaluable patients with complicated skin and skin structure infections are presented in Table 6 below.

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

Pathogen	Tigecycline 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)
Methicillin-susceptible Staphylococcus aureus (MSSA)[b]	124/137 (90.5)	113/120 (94.2)
Methicillin-resistant Staphylococcus aureus (MRSA)	79/95 (83.2)	46/57 (80.7)
CA-MRSA[c]	13/20 (65.0)	10/12 (83.3)
Streptococcus agalactiae	8/8 (100)	11/14 (78.6)
Streptococcus anginosus grp.[d]	17/21 (81.0)	9/10 (90)
Streptococcus pyogenes	31/32 (96.9)	24/27 (88.9)
Bacteroides fragilis	7/9 (77.8)	4/5 (80)

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

Complicated Intra-abdominal Infections

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

Table 7: Clinical Cure Rates from Two Pivotal Studies in Complicated Intra-abdominal Infections

	Tigecycline[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 test of cure (TOC) by pathogen in microbiologically evaluable patients with complicated intra-abdominal infections are presented in Table 8.

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

Pathogen	Tigecycline n / N (%)	Imipenem/ Cilastatin n / N (%)
Citrobacter freundii	12/16 (75.0)	3/4 (75.0)

Pathogen	Tigecycline n / N (%)	Imipenem/ Cilastatin n / N (%)
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)[c]	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 (66.6)
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 bacteraemia.
[d] Includes *Streptococcus anginosus, Streptococcus intermedius*, and *Streptococcus constellatus*.

Methicillin-Resistant Staphylococcus Aureus (MRSA)

Tigecycline was evaluated in adults for the treatment of various serious infections (cIAI, cSSSI, and other infections) due to MRSA in Study 307.

Study 307 was a randomised, double-blind, active-controlled, multinational, multicentre study evaluating tigecycline (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 methicillin-resistant *Staphylococcus aureus* (MRSA). Patients 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 microbiologically evaluable (ME) and the microbiologic modified intent-to-treat (m-mITT) patients. See Table 9 for MRSA.

Table 9: Clinical Cure Rates from Resistant Pathogen Study 307[a] for MRSA after 7 to 28 Days of Therapy

	Tigecycline[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)	20/23 (87.0)

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

Note: In this study, Tigecycline was also compared to Linezolid (600 mg IV every 12 hours) for the treatment of infections due to vancomycin resistant *Enterococcus* (VRE). Numbers recruited for the trial were small, however clinical cure was reported in 3/3 ME subjects and 3/8 m-mITT subjects treated with Tigecycline

5.2 Pharmacokinetic Properties

The mean pharmacokinetic parameters of tigecycline for this dosage regimen after single and multiple intravenous doses are summarised in Table 10.

Table 10: Mean (CV%) Pharmacokinetic Parameters of Tigecycline

	Single dose 100 mg	**Multiple dose[c] 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, 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_{0-12h} (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·hr/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 (8.6-fold, n=1) and colon (2.1-fold, n=5). The concentration of tigecycline in these tissues after multiple doses has not been studied.

Biotransformation

Tigecycline is not extensively metabolised. *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 faeces, 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 faeces and urine following administration of ^{14}C-tigecycline indicates that 59% of the dose is eliminated by biliary/faecal 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.

Special Populations

Hepatic Impairment

In a study comparing 10 patients with mild hepatic impairment (Child Pugh A), 10 patients with moderate hepatic impairment (Child Pugh B), and five patients with severe hepatic impairment (Child Pugh C) to 23 age- and weight-matched healthy control subjects, the single-dose pharmacokinetic disposition of tigecycline was not altered in patients with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25%, and the half-life of tigecycline was prolonged by 23% in patients with moderate hepatic impairment (Child Pugh B). In addition, systemic clearance of tigecycline was reduced by 55%, and the half-life of tigecycline was prolonged by 43% in patients with severe hepatic impairment (Child Pugh C).

Based on the pharmacokinetic profile of tigecycline, no dosage adjustment is warranted in patients with mild-to-moderate hepatic impairment (Child Pugh A and Child Pugh B). However, in patients with severe hepatic impairment (Child Pugh C), the 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 Section 4.2 Hepatic Impairment).

Renal Impairment

A single-dose study compared six subjects with severe renal impairment (creatinine clearance $Cl_{Cr} \leq 30$ mL/min), four end stage renal disease patients receiving tigecycline 2 hours before haemodialysis, four end stage renal disease patients receiving tigecycline after haemodialysis, and six healthy control subjects. The pharmacokinetic profile of tigecycline was not altered in any of the renally impaired patient groups, nor was tigecycline removed by haemodialysis. No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing haemodialysis (see Section 4.2 Renal Impairment).

Elderly

No overall differences in pharmacokinetics were observed between healthy elderly subjects (n=15, age 65-75; n=13, age >75), and younger subjects (n=18) receiving a single, 100 mg dose of tigecycline Therefore, no dosage adjustment is necessary based on age.

Children

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

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.

5.3 Preclinical Safety Data

Genotoxicity

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.

Carcinogenicity

Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of tigecycline.

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 oestrus cycles at exposures up to 4.7 times the human daily dose based on AUC.

In preclinical safety studies, ^{14}C-labelled 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose monohydrate

Hydrochloric acid

Sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

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

Tygacil is compatible with the following drugs or diluents when administered simultaneously through the same line: amikacin, dobutamine, dopamine HCl, gentamicin, haloperidol, Lactated Ringer's, lignocaine HCl, metoclopramide, morphine, noradrenaline, piperacillin/tazobactam (EDTA formulation), potassium chloride, propofol, ranitidine HCl, theophylline and tobramycin.

The following drugs should not be administered simultaneously through the same line as tigecycline: amphotericin B, chlorpromazine, esomeprazole, omeprazole, methylprednisolone, diazepam and voriconazole.

6.3 Shelf Life

24 months.

Reconstitution and further dilution of Tygacil must be performed immediately before use.

Once reconstituted in the IV bag, Tygacil may be stored below 25°C for up to 6 hours, or refrigerated at 2°C to 8°C for up to 24 hours.

6.4 Special Precautions for Storage

Tygacil should be stored below 25°C prior to reconstitution.

For storage conditions after reconstitution of the medicinal product, see Section 6.3.

6.5 Nature and Contents of Container

Tygacil is supplied in single-dose, 5 mL glass vials containing 50 mg tigecycline lyophilised powder for intravenous infusion.

6.6 Special Precautions for Disposal and Other Handling

The lyophilised powder should be reconstituted with 5.3 mL of 0.9% Sodium Chloride Injection, USP, or 5% Glucose 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, tigecycline may be stored below 25°C for up to 6 hours, or refrigerated at 2°C to 8°C for up to 24 hours.

Tygacil contains no antimicrobial preservative. It is for single use in one patient only. Discard any residue.

Tygacil may be administered intravenously through a dedicated line through a Y site. If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of tigecycline with either 0.9% Sodium Chloride Injection USP, or 5% Glucose 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 Section 6.2).

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand, 1140.
Toll Free Number: 0800 736 363.
www.pfizermedicalinformation.co.nz

9. DATE OF FIRST APPROVAL

11 December 2008.

10. DATE OF REVISION OF TEXT

15 January 2025.

Summary table of changes

Section changed	Summary of new information
4.8	Addition of class effect statement on ‘fixed drug eruptions’ and update to New Zealand Adverse Reactions Reporting Form website link
5.1	Update to ATC code
8	Addition of Pfizer website address

® Registered trademark