NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Tigecycline Juno 50 mg Powder for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOISTION

Each 5 mL glass vials of Tigecycline 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 to orange-red lyophillised cake or powder.
The reconstituted solution is orange-red, essentially free of particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tigecycline 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

Tigecycline 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

Tigecycline is contraindicated for use in patients who have known hypersensitivity 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 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). Tigecycline is not approved for the treatment of hospital-acquired pneumonia (including ventilator-associated pneumonia), community-acquired pneumonia or diabetic foot infections.

Anaphylaxis/Anaphylactoid Reactions

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

Hypersensitivity to Tetracycline-class Antibiotics

Tigecycline 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.

Acute Pancreatitis

Acute pancreatitis, which can be fatal, has occurred (frequency: uncommon) in association with tigecycline treatment (see **Section 4.8**). The diagnosis of acute pancreatitis should be considered in patients taking tigecycline who develop clinical symptoms, signs, or laboratory abnormalities suggestive of acute pancreatitis. Cases have been reported in patients without known risk factors for pancreatitis. Patients usually improve after tigecycline discontinuation. Consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis.

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 (Lomotil) 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 Interactions with Other Medicines and Other Forms of Interactions

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), coadministration of P-gp inhibitors (e.g., ketoconazole or cyclosporine) 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 tigecycline.

4.6 Fertility, Pregnancy and Lactation

Fertility

Tigecycline did not affect mating or fertility in rats at exposures up to 5 times the human daily dose based on AUC. In female rats, there were no compound-related effects on ovaries or oestrus cycles at exposures up to 5 times the human daily dose based on AUC.

Pregnancy

Pregnancy Category D.

Tigecycline may cause fetal harm when administered to a pregnant woman. In preclinical safety studies, ^{14}C-labelled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures.

Tigecycline was not teratogenic in the rat or rabbit. The administration of tigecycline was associated with slight reductions in fetal weights and an increased incidence of minor skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1.5 times the human daily dose based on AUC in rats and rabbits, respectively. An increased incidence of fetal loss was observed at exposures of 1.5 times the human daily dose based on AUC in rabbits, at dosages producing minimal maternal toxicity.

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 foetus.

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

Lactation

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.

It is not known whether this drug is excreted in human milk. Because tetracyclines are present in milk of lactating women who are taking a drug in this class, caution should be exercised when tigecycline is administered to a nursing woman.

4.7 Effects on Ability to Drive and Use Machinery

Tigecycline 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	**Tigecycline[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
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

Table 1: Incidence (%) of Treatment Emergent Adverse Events Through Test of Cure		
Body System	**Tigecycline[a]**	**Comparators[b]**
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		
Bilirubinaemia	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 Tigecycline-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.

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

System Organ Class	Adverse Reaction
Infections and Infestations	
Common (≥ 1 % and < 10 %)	Abscess, infections
Uncommon (≥ 0.1% and < 1%)	Sepsis/septic shock
Blood and Lymphatic System Disorders	
Common (≥ 1 % and < 10 %)	Prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time (PT)
Uncommon (≥ 0.1% and < 1%)	Increased international normalised ratio (INR)
Metabolism and Nutrition Disorders	
Common (≥ 1 % and < 10 %)	Hypoproteinaemia
Nervous system Disorders	
Common (≥ 1 % and < 10 %)	Dizziness
Vascular Disorders	
Common (≥ 1 % and < 10 %)	Phlebitis
Uncommon (≥ 0.1% and < 1%)	Thrombophlebitis
Gastrointestinal Disorders	
Very common (≥ 10%)	Nausea, vomiting, diarrhoea
Common (≥ 1 % and < 10 %)	Anorexia, abdominal pain, dyspepsia
Hepatobiliary Disorders	
Common (≥1 % and < 10 %)	Bilirubinaemia,
General Disorders and Administration Site Conditions	
Common (≥ 1 % and < 10 %)	Headache
Uncommon (≥ 0.1% and < 1%)	Injection site inflammation, injection site pain, injection site reaction, injection site oedema, injection site phlebitis
Investigation	
Common (≥ 1 % and < 10 %)	Elevated amylase in blood, elevated aspartate aminotransferase (AST) in blood, and elevated blood alanine aminotransferase (ALT) in blood, increased blood urea

In Phase 3 clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with tigecycline (6.7%) vs. comparator (4.6%). Significant differences in sepsis/septic shock with tigecycline (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 tigecycline vs. comparator respectively.

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.

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 tigecycline 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 Tigecycline. 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:

Blood and Lymphatic System Disorders	
Common	Thrombocytopenia
Frequency undetermined	Hypofibrinogenaemia
Immune system disorders	
Frequency undetermined	Anaphylaxis/anaphylactoid reactions
Metabolism and Nutrition Disorders	
Common	Hypoglycaemia
Respiratory, Thoracic and Mediastinal Disorders	
Common	Pneumonia
Gastrointestinal Disorders	
Uncommon	Acute pancreatitis
Hepatobiliary Disorders	
Uncommon	Jaundice
Frequency undetermined	Hepatic cholestasis
Skin and Subcutaneous Tissue Disorders	
Frequency undetermined	Severe skin reactions, including Stevens-Johnson Syndrome
General Disorders and Administration Site Conditions	
Common	Healing abnormal, injection site reaction

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://nzphvc.otago.ac.nz/reporting/.

4.9 Overdosage

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

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. Tigecycline is not affected by the major tetracycline resistance mechanism of

ribosomal protection and is not affected by many efflux systems. Accordingly, tigecycline has demonstrated *in vitro* and *in vivo* activity against a broad spectrum of bacterial pathogens.

There has currently been limited 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).

Susceptibility Tests

Dilution or Diffusion techniques, either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method. Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood 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, which 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 in the blood reaches the concentrations usually achievable; other therapy should be selected.

Table 3: 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	≤1[a]	-	-	≥21	-	-
Moraxella catarrhalis	≤0.12[a]	-	-	≥27	-	-
Anaerobes[c]	≤4	8	≥16	n/a	n/a	n/a

[a] The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results suggestive of "Non-susceptible" 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.

Microbiology

Tigecycline has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in **Section 4.1**.

Gram-positive aerobes

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 (includes *S. anginosus, S .intermedius, S. constellatus*)
Streptococcus pyogenes
Streptococcus pneumoniae (penicillin-susceptible isolates)

Gram-negative aerobes

Citrobacter freundii
Enterobacter cloacae
Escherichia coli (including ESBL producing strains)
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae (including ESBL producing strains)
Legionella pneumophila
Moraxella catarrhalis

Anaerobic bacteria

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

Atypical bacteria

Chlamydia pneumoniae
Mycoplasma pneumoniae

In vitro data are available for the following organisms, but their clinical significance is unknown. The *in vitro* minimum inhibitory concentrations (MIC) of 90% or more of these microorganisms were 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.

Gram-positive aerobes

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

Gram-negative aerobes

Acinetobacter calcoaceticus/baumannii complex
Aeromonas hydrophila
Citrobacter koseri
Enterobacter aerogenes
Haemophilus parainfluenzae
Klebsiella pneumoniae (including AmpC producing strains)
Pasteurella multocida
Salmonella enterica ser. *Enteritidis*
Salmonella enterica ser. *Paratyphi*
Salmonella enterica ser. *Typhi*
Salmonella enterica ser. *Typhimurium*
Serratia marcescens
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Shigella sonnei
Stenotrophomonas maltophilia

Anaerobic bacteria

Bacteroides ovatus
Clostridium difficile
Peptostreptococcus spp.
Porphyromonas spp.
Prevotella spp.

Atypical bacteria

Mycobacterium abscessus
Mycobacterium chelonae
Mycobacterium fortuitum

Resistant

Gram-negative aerobes:

Pseudomonas aeruginosa and Proteeae (Proteus spp., Providencia spp. and Morganella spp.)

Anaerobic bacteria:

No naturally occurring species have been found to be inherently resistant to tigecycline.

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.

Acquired resistance to tigecycline has been demonstrated in several clinical isolates of Enterobacteriaceae due to overexpression of the AcrAB efflux system, a multi-drug efflux pump.

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

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 (1g IV every 12 hours)/aztreonam (2g 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 4 below.

Table 4: Clinical Cure Rates from Two Pivotal Studies in Complicated Skin and Skin Sructure 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 5 below.

Table 5: 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)

Pathogen	Tigecycline n / N (%)	Vancomycin/ Aztreonam n / N (%)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)[b]	124/137 (90.5)	113/120 (94.2)
Methicillin-resistant *Staphylococcus aureu* (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 6 below.

Table 6: 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 7.

Table 7: 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)
Enterobacter cloacae	15/17 (88.2)	16/17 (94.1)
Escherichia coli	284/336 (84.5)	297/342 (86.8)

Pathogen	Tigecycline n / N (%)	Imipenem/ Cilastatin n / N (%)
Klebsiella oxytoca	19/20 (95.0)	17/19 (89.5)
Klebsiella pneumoniaeb	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, multicenter 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 7 for MRSA.

Table 8: 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 **cIAI** **cSSSI**	70/86 (81.4) 13/14 (92.9) 51/59 (86.4)	26/31 (83.9) 4/4 (100.0) 20/23 (87.0)
m-mITT **cIAI** **cSSSI**	75/100 (75.0) 13/15 (86.7) 55/70 (78.6)	27/33 (81.8) 5/6 (83.3) 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

	Tigecycline[b] n/N (%)	Vancomycin[c] n/N (%)
[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 9.

Table 9: Mean (CV%) Pharmacokinetic Parameters of Tigecycline

	Single dose 100mg	Multiple dose[c] 50 mg q12h
Cmax (µg/mL)[a]	1.45 (22%)	0.87 (27%)
Cmax (µg/mL)[b]	0.90 (30%)	0.63 (15%)
AUC (µg·h/mL)	5.19 (36%)	-
AUC0-24h (µg·h/mL)	-	4.70 (36%)
Cmin (µg/mL)	-	0.13 (59%)
t½ (h)	27.1 (53%)	42.4 (83%)
CL (L/h)	21.8 (40%)	23.8 (33%)
CLr (mL/min)	38.0 (82%)	51.0 (58%)
Vss (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 $AUC_{0\text{-}12h}$ (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·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.

6. PHARMACEUTICAL PARTICUALRS

6.1 List of Excipients

L-Arginine.
Hydrochloric acid (for pH adjustment)
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.

Tigecycline 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 Tigecycline must be performed immediately before use.

Once reconstituted in the IV bag, 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.

6.4 Special Precautions for Storage

Tigecycline 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

Tigecycline is supplied in single-dose, 5 mL Type I 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.

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

Tigecycline 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

Juno Pharmaceuticals NZ Limited

9. DATE OF FIRST APPROVAL

19 December 2019

10. DATE OF REVISION OF TEXT

08 January 2020

SUMMARY OF REVISION OF THE TEXT

Section changed	Summary of new information
8	Update sponsor details