mg daily) when administered in healthy adults. Digoxin did not affect the pharmacokinetic profile of tigecycline. Therefore, no dosage adjustment is necessary when tigecycline is administered with digoxin.
In vitro, no antagonism has been observed between tigecycline and other commonly used antibiotic classes.
Concurrent use of antibiotics with oral contraceptives may render oral contraceptives less effective.
Based on in vitro, tigecycline is a P-gp substrate. Co-administration of P-gp inhibitors (e.g., ketoconazole or cyclosporine) or P-gp inducers (e.g., rifampicin) could affect the pharmacokinetics of tigecycline.

ADVERSE EFFECTS
Summary of safety profile
The most common medicinal product-related treatment emergent adverse reactions were reversible nausea and vomiting, which usually occurred early (on treatment days 1-2) and were generally mild or moderate in severity.
Adverse reactions reported with tigecycline, are tabulated below.

Table 2. Tabulated list of adverse reactions

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known (cannot be estimated from available data)
Infections and infestations		sepsis/septic shock, pneumonia, abscess, infections			
Blood and lymphatic system disorders		prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time (PT)	thrombocytopenia, increased international normalised ratio (INR)	Hypofibri-nogenaemia	
Immune system disorders					anaphylaxis/ anaphylactoid reactions*
Metabolism and nutrition disorders		hypoglycaemia, hypoproteinaemia			
Nervous system disorders		dizziness			
Vascular disorders		phlebitis	thrombophlebitis		
Gastrointestinal disorders	nausea, vomiting diarrhoea	abdominal pain, dyspepsia, anorexia	acute pancreatitis		
Hepatobiliary disorders		elevated aspartate aminotransferase (AST) in serum, and elevated alanine aminotransferase (ALT) in serum, hyperbilirubinaemia	jaundice, liver injury, mostly cholestatic		hepatic failure*
Skin and subcutaneous tissue disorders		pruritus, rash			severe skin reactions, including Stevens-Johnson Syndrome*
General disorders and administration site conditions		impaired healing, injection site reaction, headache	injection site inflammation, injection site pain, injection site oedema, injection site phlebitis		
Investigations		elevated amylase in serum, increased blood urea nitrogen (BUN)			

*ADR identified post-marketing

Description of selected adverse reactions
Antibiotic class effects
Pseudomembranous colitis which may range in severity from mild to life threatening.
Overgrowth of non-susceptible organisms, including fungi.

Tetracycline class effects
Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. Tetracycline class adverse reactions may include photosensitivity, pseudotumour cerebri, pancreatitis, and antianabolic action which has led to increased BUN, azotaemia, acidosis, and hyperphosphataemia.

Tigecycline may be associated with permanent tooth discolouration if used during tooth development.

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

Ability to Drive and Use Machines
Dizziness may occur and this may have an effect on driving and use of machines.

SYMPTOMS AND TREATMENT OF OVERDOSE
No specific information is available on the treatment of overdosage. Intravenous administration of tigecycline at a single dose of 300 mg over 60 minutes in those who are healthy resulted in an increased incidence of nausea and vomiting. Tigecycline is not removed in significant quantities by haemodialysis

INSTRUCTIONS FOR USE
The lyophilized powder should be reconstituted with 5.0 mL of 0.9% Sodium Chloride Injection, or 5% Dextrose Injection or Lactated Ringer's Solution for Injection , to achieve a concentration of 10 mg/mL of tigecycline. The vial should be gently swirled until the drug dissolves. Thereafter, 5 ml of the reconstituted solution should be immediately withdrawn from the vial and added to a 100 ml intravenous bag for infusion or other suitable infusion container (e.g., glass bottle).

PRESENTATION
10 ml glass vial is placed in a plastic tray and then packed in a carton with pack insert.

STORAGE AND HANDLING
Store below 30°C. Keep out of reach of children.

STABILTIY/STORAGE:
Prior to administration, TYLIN should be stored below 30°C. Once reconstituted with 5.0 mL of 0.9% Sodium Chloride Injection, or 5% Dextrose Injection or Lactated Ringer's Solution for Injection,,TYLIN may be stored at 25°C for up to 24 hours (up to 6 hours in the vial and remaining time in the IV bag). Alternatively, TYLIN may be refrigerated at 2°C to 8° C for upto 48 hours following immediate transfer of the reconstituted solution in to the IV bag.
Reconstituted solution must be transfered and further diluted for IV infusion.

PLEASE DO NOT USE WATER FOR INJECTION FOR RECONSTITUTION.

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Manufactured by:
GUFIC®
BIOSCIENCES LIMITED
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℞ *For the use only of a Registered Medical Practitioner of a Hospital or a Laboratory*

TYLIN

Tigecycline Powder for Solution for Infusion 50 mg / vial

Lyophilized
FOR I.V. INFUSION ONLY

COMPOSITION
Each vial contains
Tigecycline USP.....50mg
Excipients.....q.s.

Appearance of powder:
Light yellowish orange lyophilized cake

Appearance of reconstituted solution:
Clear, yellow to orange colour solution.

CLINICAL PHARMACOLOGY
Pharmacokinetics

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

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

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

	Single Dose 100 mg	Multiple[a] Dose 100 mg
C_{max} (µg/mL)b	1.45 (22%)	0.87 (27%)
C_{max} (µg/mL)c	0.90 (30%)	0.63 (15%)
AUC (µg·h/mL)	5.19 (36%)	- -
$AUC_{0\text{-}24h}$ (µg·h/mL)	- -	4.70 (36%)
C_{min} (µg/mL)	- -	0.13 (59%)
t½ (h)	27.1 (53%)	42.4 (83%)
CL (L/h)	21.8 (40%)	23.8 (33%)
CL_r (mL/min)	38.0 (82%)	51.0 (58%)
V_{ss} (L)	568 (43%)	639 (48%)

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

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

Metabolism
Tigecycline is not extensively metabolized.

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

Specific Population
Hepatic impairment
The single-dose pharmacokinetic disposition of tigecycline was not altered in those with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25 % and 55 % and the half-life of tigecycline was prolonged by 23% and 43 % in those with moderate or severe hepatic impairment (Child Pugh B and C), respectively. In those with severe hepatic impairment (Child Pugh C), the dose of tigecycline should be reduced to 100 mg followed by 25mg every 12 hours.

Use in those with Renal Impairment
No dosage adjustment of TYLIN is necessary in those with renal impairment or in patients undergoing hemodialysis

Geriatric Patients
No dosage adjustment is necessary based on age.

Microbiology
Mechanism of Action
Tigecycline, a glycylcycline, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. Tigecycline carries a glycylamido moiety attached to the 9-position of minocycline. The substitution pattern is not present in any naturally occurring or semisynthetic tetracycline and imparts certain microbiologic properties to tigecycline. In general, tigecycline is considered bacteriostatic; however, At 4 times the minimum inhibitory concentration (MIC), a 2-log reduction in colony counts was observed with tigecycline against Enterococcus spp., Staphylococcus aureus, and Escherichia coli.**

Mechanism of Resistance
Tigecycline is able to overcome the two major tetracycline resistance mechanisms, ribosomal protection and efflux. Cross-resistance between tigecycline and minocycline-resistant isolates among the Enterobacteriaceae due to multi-drug resistance (MDR) efflux pumps has been shown. There is no target-based cross-resistance between tigecycline and most classes of antibiotics.
Tigecycline is vulnerable to chromosomally-encoded multidrug efflux pumps of Proteeae and Pseudomonas aeruginosa. Pathogens of the family Proteeae (Proteus spp., Providencia spp., and Morganella spp.) are generally less susceptible to tigecycline than other members of the Enterobacteriaceae. Decreased susceptibility in both groups has been attributed to the overexpression of the non-specific AcrAB multi-drug efflux pump. Decreased susceptibility in Acinetobacterbaumannii has been attributed to the overexpression of the AdeABC efflux pump.
Interaction with Other Antimicrobials
In vitro studies have not demonstrated antagonism between tigecycline and other commonly used antibacterials.

Tigecycline has been shown to be active against most of the following bacteria, both in vitro and in clinical infections.

Breakpoints
Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:
Staphylococcus spp. S ≤ 0.5 mg/L and R > 0.5 mg/L
Streptococcus spp. other than S. pneumoniae S ≤ 0.25 mg/L and R > 0.5 mg/L
Enterococcus spp. S ≤ 0.25 mg/L and R > 0.5 mg/L
Enterobacteriaceae S ≤ 1(^) mg/L and R > 2 mg/L
(^)Tigecycline has decreased in vitro activity against Proteus, Providencia, and Morganella spp.
For anaerobic bacteria there is 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. It should be noted that the MIC distributions for organisms of the genera Bacteroides and Clostridium are wide and may include values in excess of 2 mg/L tigecycline.
There is limited evidence of the clinical efficacy of tigecycline against enterococci. However, polymicrobial intra-abdominal infections have shown to respond to treatment with tigecycline.

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

Pathogen
Commonly Susceptible Species
Gram-positive Aerobes
Enterococcus spp.†
Staphylococcus aureus*
Staphylococcus epidermidis
Staphylococcus haemolyticus
Streptococcus agalactiae*
Streptococcus anginosus group* (includes S. anginosus, S. intermedius and S. constellatus)
Streptococcus pyogenes*
Viridans group streptococci
Gram-negative Aerobes
Citrobacterfreundii*
Citrobacterkoseri
Escherichia coli*
Klebsiellaoxytoca*
Anaerobes
Clostridium perfringens †
Peptostreptococcus spp.†
Prevotella spp.

Species for which acquired resistance may be a problem
Gram-negative Aerobes
Acinetobacterbaumannii
Burkholderiacepacia
Enterobacteraerogenes
Enterobacter cloacae*
Klebsiellapneumoniae*
Morganellamorganii
Proteus spp.
Providencia spp.
Pathogen
Serratiamarcescens
Stenotrophomonasmaltophilia
Anaerobes
Bacteroidesfragilis group†

Inherently resistant organisms
Gram-negative Aerobes
Pseudomonas aeruginosa
*denotes species against which it is considered that activity has been satisfactorily demonstrated.
† see section, Breakpoints above

INDICATIONS AND USAGE
TYLIN is a tetracycline-class antibacterial indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the conditions listed below for patients 18 years of age and older:
Complicated Skin and Skin Structure Infections
Complicated skin and skin structure infections caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae, Streptococcus anginosus grp.* (includes *S. anginosus, S. intermedius* and *S. constellatus*), *Streptococcus pyogenes, Enterobacter cloacae, Klebsiella pneumoniae* and *Bacteroides fragilis*.

Complicated Intra-abdominal Infections
Complicated intra-abdominal infections caused by *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus grp.* (Includes *S. anginosus, S. intermedius* and *S. constellatus*), *Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens* and *Peptostreptococcus micros.*

Usage
To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYLIN and other antibacterial drugs, TYLIN should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

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

DOSAGE AND ADMINISTRATION
General Dosage and Administration
Reconstitution with 5.0 mL of 0.9% Sodium Chloride Injection, or 5% Dextrose Injection or Lactated Ringer's Solution for Injection
The recommended dosage regimen for TYLIN is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous infusions of TYLIN should be administered over approximately 30 to 60 minutes every 12 hours.
The recommended duration of treatment with TYLIN 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.

Patients With Hepatic Impairment
No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of TYLIN should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response.

Use in children
Clinical trials to establish the safety and effectiveness of tigecycline in patients under 18 years of age have not been conducted. Therefore, use in patients under 18 years of age is not recommended.

TYLIN may be administered intravenously through a dedicated line or through a Y-site. If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of TYLIN with 5.0 mL of 0.9% Sodium Chloride Injection, or 5% Dextrose Injection or Lactated Ringer's Solution for Injection should be made with an infusion solution compatible with tigecycline and with any other drug(s) administered via this common line.

The lyophilized powder should be reconstituted with 5.0 mL of 0.9% Sodium Chloride Injection, or 5% Dextrose Injection or Lactated Ringer's Solution for Injection to achieve a concentration of 10 mg/mL of tigecycline. The vial should be gently swirled until the drug dissolves. Thereafter, 5 ml of the reconstituted solution should be immediately withdrawn from the vial and added to a 100 ml intravenous bag for infusion or other suitable infusion container (e.g., glass bottle).

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

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

This medicinal product is for single use only; any unused medicinal product or waste material should be disposed of in accordance with local requirements.

CONTRAINDICATIONS
TYLIN is contraindicated for use in those who have known hypersensitivity to tigecycline

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
In complicated skin and soft tissue infections (cSSTI), complicated intra-abdominal infections (cIAI), diabetic foot infections, nosocomial pneumonia and in resistant pathogens, a numerically higher mortality rate among those treated with tigecycline has been observed as compared to the comparator treatment. The causes of these findings remain unknown, but poorer efficacy and safety than the comparators cannot be ruled out.

Superinfection
In those with cIAI, impaired healing of the surgical wound has been associated with superinfection. For those developing impaired healing, they should be monitored for the detection of superinfection. Those who develop superinfections, in particular nosocomial pneumonia, appear to be associated with poorer outcomes. They should be closely monitored for the development of superinfection. If a focus of infection other than cSSTI or cIAI is identified after initiation of tigecycline therapy consideration should be given to instituting alternative antibacterial therapy that has been demonstrated to be efficacious in the treatment of the specific type of infection(s) present.

Anaphylaxis
Anaphylaxis/anaphylactoid reactions, potentially life-threatening, have been reported with tigecycline.

Hepatic failure
Cases of liver injury with a predominantly cholestatic pattern have been reported in those receiving tigecycline treatment, including some cases of hepatic failure with a fatal outcome. Although hepatic failure may occur in those treated with tigecycline due to the underlying conditions or concomitant medicinal products, a possible contribution of tigecycline should be considered.

Tetracycline class antibiotic
Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. Tigecycline may have adverse reactions similar to tetracycline class antibiotics. Such reactions may include photosensitivity, pseudotumorcerebri, pancreatitis, and anti anabolic action which has led to increased BUN, azotaemia, acidosis, and hyperphosphataemia.

Pancreatitis
Acute pancreatitis, which can be serious, has occurred (frequency: uncommon) in association with tigecycline treatment. The diagnosis of acute pancreatitis should be considered in those taking tigecycline who develop clinical symptoms, signs, or laboratory abnormalities suggestive of acute pancreatitis. Most of the reported cases developed after at least one week of treatment. Cases have been reported in those without known risk factors for pancreatitis. They usually improve after tigecycline discontinuation. Consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis.

Underlying diseases
Experience in the use of tigecycline for treatment of infections in those with severe underlying diseases is limited.
In patients with diabetic foot infection, showed that tigecycline was less effective than comparator, therefore, tigecycline is not recommended for use in them.
Consideration should be given to the use of combination antibacterial therapy whenever tigecycline is to be administered to those severely ill with cIAI secondary to clinically apparent intestinal perforation or in those with incipient sepsis or septic shock.
The effect of cholestasis in the pharmacokinetics of tigecycline has not been properly established. Biliary excretion accounts for approximately 50 % of the total tigecycline excretion. Therefore, those presenting with cholestasis should be closely monitored.
Prothrombin time or other suitable anticoagulation test should be used for monitoring if tigecycline is administered with anticoagulants.
Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in those who present with diarrhoea during or subsequent to the administration of any antibacterial agent.
The use of tigecycline may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy.
Tigecycline have shown bone discolouration in rats. Tigecycline may be associated with permanent tooth discolouration in humans if used during tooth development.

Pregnancy
There are no or limited amount of data from the use of tigecycline in pregnant women. It is shown that tigecycline shows reproductive toxicity in animals. The potential risk for humans is unknown. As it is known for tetracycline class antibiotics, tigecycline may also induce permanent dental defects (discolouration and enamel defects) and a delay in ossification processes in foetuses, exposed in utero during the last half of gestation, and in children under eight years of age due to the enrichment in tissues with a high calcium turnover and formation of calcium chelate complexes. Tigecycline should not be used during pregnancy unless the clinical condition of the woman requires treatment with tigecycline.

Breast feeding
It is unknown whether tigecycline/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of tigecycline/metabolites in milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from tigecycline therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
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.

Interactions with Other Medicaments
Interaction studies have only been performed in adults.
Concomitant administration of tigecycline and warfarin (25 mg single-dose) resulted in a decrease in clearance of R-warfarin and S-warfarin by 40 % and 23 %, and an increase in AUC by 68 % and 29 %, respectively. The mechanism of this interaction is still not elucidated. Available datadoes not suggest that this interaction may result in significant INR changes. However, since tigecycline may prolong both prothrombin time (PT) and activated partial thromboplastin time (aPTT), the relevant coagulation tests should be closely monitored when tigecycline is co-administered with anticoagulants. Warfarin did not affect the pharmacokinetic profile of tigecycline.
Tigecycline is not extensively metabolised. Therefore, clearance of tigecycline is not expected to be affected by active substances that inhibit or induce the activity of the CYP450 isoforms. In vitro, tigecycline is neither a competitive inhibitor nor an irreversible inhibitor of CYP450 enzymes.
Tigecycline in recommended dosage did not affect the rate or extent of absorption, or clearance of digoxin (0.5 mg followed by 0.25