PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

TYCLIN™, 50 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TYCLIN vial contains 50 mg of tigecycline, as tigecycline dihydrate. After reconstitution, 1 mL solution contains 10 mg of tigecycline.

Contains sugar (lactose monohydrate).

Excipients with known effect

Each vial contains 106 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile powder for solution for infusion

TYCLIN is an orange lyophilised cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prescribers must adhere to the principles of antibiotic stewardship.

TYCLIN is indicated for the treatment of the following severe life-threatening infections in adults:

- Complicated skin and soft tissue infections (excluding diabetic foot infections) caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-

susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates*), Streptococcus agalactiae*, *Streptococcus anginosus* group (includes *S. anginosus, S. intermedius*, and *S. constellatus), Streptococcus pyogenes* and *Bacteroides fragilis.*

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

4.2 Posology and method of administration

Posology

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

The recommended duration of treatment with TYCLIN 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.

Special populations

Patients with renal impairment

No dosage adjustment of TYCLIN is necessary in patients with renal impairment or in patients undergoing haemodialysis (see section 5.2).

Patients with hepatic impairment

No dosage adjustment of TYCLIN is necessary in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B).

Based on the pharmacokinetic profile of TYCLIN in patients with severe hepatic impairment (Child Pugh C), the dose of TYCLIN 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).

Elderly population

No dosage adjustment is necessary in elderly patients (see section 4.4).

Paediatric population

Clinical trials to establish the safety and effectiveness of TYCLIN in patients under 18 years of age have not been conducted. Therefore, use in patients under 18 years of age is not recommended (see section 4.4).

Method of administration

Intravenous infusion.

For instructions on reconstitution & dilution of the medicine before administration, see section 6.6.

4.3 Contraindications

TYCLIN is contraindicated for use in

- patients who have known hypersensitivity to tigecycline or to any of the excipients of TYCLIN (listed in section 6.1);
- patients hypersensitive to tetracycline class antibiotics may be sensitive to TYCLIN;
- pregnancy and lactation.

4.4 Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship.

An increase in all-cause mortality has been reported in a pooled analysis across Phase 3 and 4 clinical studies in patients treated with tigecycline, compared to the 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.

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

Anaphylaxis

Anaphylaxis/anaphylactoid reactions have been reported with tigecycline (contained in TYCLIN) and may be life-threatening (see sections 4.3 and 4.8).

Hospital Associated Pneumonia

TYCLIN should not be used in hospital associated pneumonia (HAP) or ventilator-associated pneumonia (VAP). The safety and efficacy of TYCLIN in patients with hospital acquired pneumonia (HAP) have not been established. In a published study of patients with hospital acquired pneumonia, patients were randomised to receive tigecycline or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. The sub-group of patients with ventilator-associated pneumonia (VAP) who received tigecycline had lower cure rates and higher mortality than the comparator. Of those patients with ventilator-associated pneumonia and bacteraemia at baseline, those who received tigecycline had greater mortality than the comparator.

Tetracycline class antibiotics

TYCLIN is contraindicated in patients with known hypersensitivity to tetracycline class antibiotics (see section 4.3).

Tigecycline as in TYCLIN is structurally similar to tetracycline class antibiotics and may have similar adverse reactions. Such reactions may include photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic action which has led to increased blood urea nitrogen (BUN), uraemia, azotaemia, acidosis, and hyperphosphataemia (see section 4.8).

Superinfection

Use of TYCLIN may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection including *Clostridium difficile* colitis occurs, appropriate measures should be taken.

It is reported that in clinical trials in cIAI patients, impaired healing of the surgical wound has been associated with superinfection. A patient developing impaired healing should be monitored for the detection of superinfection (see section 4.8).

Patients who develop superinfections, in particular nosocomial pneumonia, appear to be associated with poorer outcomes. Patients 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, as in TYCLIN, 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.

Pseudomembranous colitis has been reported with tigecycline, as in TYCLIN. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of TYCLIN (see section 4.8).

Complicated abdominal infections

Caution should be exercised when considering TYCLIN monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. More patients treated with tigecycline than patients treated with comparator developed sepsis/septic shock. The relationship of this outcome to treatment cannot be established.

Hepatic failure

Cases of liver injury with a predominantly cholestatic pattern have been reported in patients treated with tigecycline, as in TYCLIN, including some cases of hepatic failure with a fatal outcome. Although hepatic failure may occur

in patients treated with tigecycline due to the underlying conditions or concomitant medicines, a possible contribution of tigecycline, as in TYCLIN, should be considered (see section 4.8).

Pancreatitis

Pancreatitis has been reported with the use of tigecycline as in TYCLIN.

Acute pancreatitis, which can be fatal, has occurred in association with tigecycline (as in TYCLIN) treatment (see section 4.8). The diagnosis of acute pancreatitis should be considered in patients receiving TYCLIN 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 patients without known risk factors for pancreatitis. Patients usually improved after tigecycline as in TYCLIN discontinuation. Cessation of the treatment with TYCLIN in cases suspected of having developed pancreatitis is advised.

Coagulopathy

TYCLIN may prolong both prothrombin time (PT) and activated partial thromboplastin time (aPTT). Additionally, hypofibrinogenaemia has been reported with the use of tigecycline. Therefore, blood coagulation parameters such as PT or other suitable anticoagulation test, including blood fibrinogen, should be monitored prior to treatment initiation with tigecycline and regularly while on treatment. Special care is recommended in seriously ill patients and in patients also using anticoagulants (see section 4.5).

Underlying diseases

Reported experience in the use of TYCLIN for treatment of infections in patients with severe underlying diseases is limited.

In reported clinical trials in cSSTI, the most common type of infection in tigecycline-treated patients was cellulitis, followed by major abscesses. Patients with severe underlying diseases, such as those that were immunocompromised, patients with decubitus ulcer infections, or patients that had infections requiring longer than 14 days of treatment (for example, necrotizing fasciitis), were not enrolled. A limited number of patients were enrolled with co-morbid factors such as diabetes, peripheral vascular disease, intravenous substance abuse, and human immunodeficiency virus (HIV)-positive infection. Limited reported experience is also available in treating patients with concurrent bacteraemia. Therefore, caution is advised when treating such patients. The results reported on a large study in patients with diabetic foot infection, showed that tigecycline was less effective than comparator, therefore, TYCLIN is not recommended for use in these patients.

In reported clinical trials in cIAI, the most common type of infection in tigecycline-treated patients was complicated appendicitis, followed by other diagnoses less commonly reported such as complicated cholecystitis, perforation of intestine, intra-abdominal abscess, gastric or duodenal ulcer perforation, peritonitis and complicated diverticulitis. Of these patients, 77,8 % had surgically-apparent peritonitis. There were a limited number of patients with severe underlying disease such as immunocompromised patients, patients with APACHE II scores > 15, or with surgically apparent multiple intra-abdominal abscesses. Limited reported experience is also available in treating patients with concurrent bacteraemia. Therefore, caution is advised when treating such patients.

Consideration should be given to the use of combination antibacterial therapy whenever tigecycline as in TYCLIN is to be administered to severely ill patients

with cIAI secondary to clinically apparent intestinal perforation or patients with incipient sepsis or septic shock (see section 4.8).

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

Pseudomembranous colitis has been reported with nearly all antibacterial medicines and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibacterial medicine (see section 4.8).

The use of tigecycline as in TYCLIN may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy (see section 4.8).

Bone/tooth discolouration

Results of studies in rats with tigecycline have shown bone discolouration. Tigecycline may be associated with permanent tooth discolouration in humans if used during tooth development (see section 4.8).

Special populations

Use in the elderly

No unexpected overall differences in safety or effectiveness have been reported in elderly patients. No dosage adjustment is necessary in elderly patients.

Excipient information

TYCLIN contains less than 1 mmol sodium (23 mg) per 5 mL of suspension, that is to say essentially 'sodium free'.

Paediatric population

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.

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 daily every 24 hours) were co-administered to healthy adults in a medicine interaction study. Tigecycline slightly decreased the C_{max} of digoxin 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 TYCLIN is administered with digoxin.

Warfarin

Concomitant administration of tigecycline (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single-dose) to healthy persons resulted in a decrease in clearance of R-warfarin and S-warfarin and an increase in AUC. Tigecycline did not significantly alter the effects of warfarin on increased international normalised ration (INR). In addition, warfarin did not affect the pharmacokinetic profile of tigecycline. However, prothrombin time (PT) or other suitable anticoagulation tests should be closely monitored when tigecycline as in TYCLIN is co-administered with warfarin.

CYP450 enzymes

In vitro studies in human liver microsomes reported that tigecycline does not inhibit metabolism mediated by any of the following six cytochrome CYP450 isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. Therefore, tigecycline as in TYCLIN is not expected to alter the metabolism of medicines metabolised by these enzymes. As tigecycline is not extensively metabolised, clearance of tigecycline is not expected to be affected by medicines that inhibit or induce the activity of these CYP450 isoforms.

P-gp inhibitors/inducers

In vitro studies using Caco-2 cells indicate that tigecycline does not inhibit digoxin flux, suggesting that tigecycline is not a P-glycoprotein (P-gp) inhibitor. This *in vitro* information is consistent with the lack of effect of tigecycline on digoxin clearance noted in the *in vivo* medicine interaction study described above.

Tigecycline is a substrate of P-gp based on an *in vitro* study using a cell line overexpressing P-gp. The potential contribution of P-gp-mediated transport to the *in vivo* disposition of tigecycline is not known. Coadministration of P-gp inhibitors (e.g., ketoconazole or ciclosporin) or P-gp inducers (e.g., rifampicin) could affect the pharmacokinetics of tigecycline as in TYCLIN.

Oral contraceptives

Concurrent use of antibiotics with oral contraceptives may reduce the efficacy of oral contraceptives.

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 TYCLIN to avoid medicine toxicity.

Interference with laboratory and other diagnostic tests

There are no reported medicine-laboratory interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

TYCLIN may cause foetal harm when administered to a pregnant woman. Results of animal studies indicate that tigecycline crosses the placenta and is found in foetal tissues.

There are no adequate and well-controlled studies of TYCLIN in pregnant women. TYCLIN should not be used during pregnancy.

Breastfeeding

Results from animal studies using ^{14}C-labeled TYCLIN indicate that TYCLIN is excreted readily via the milk of lactating rats. It is not known whether this medicine is excreted in human milk. Therefore, TYCLIN should not be used during breastfeeding.

Fertility

The effects of tigecycline on fertility in humans have not been studied.

4.7 Effects on ability to drive and use machines

Dizziness may occur and this may have an effect on driving and use of machines (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

The most frequent medicine-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.

Tabulated list of adverse reactions

System Organ Class/ Frequency	**Adverse reaction**
Infections and infestations	
Frequent:	Sepsis/septic shock, pneumonia, abscess, infections
Blood and lymphatic system disorders	
Frequent:	Prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time (PT)
Less frequent:	Thrombocytopenia, increased international normalised ratio (INR), hypofibrinogenaemia
Immune system disorders	
Frequency unknown:	Anaphylaxis/ anaphylactoid reactions
Metabolism and nutrition disorders	
Frequent:	Hypoglycaemia, hypoproteinaemia
Nervous system disorders	
Frequent	Dizziness

Vascular disorders	
Frequent	Phlebitis
Less frequent	Thrombophlebitis
Gastrointestinal disorders	
Frequent	Nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, anorexia
Less frequent	Acute pancreatitis
Hepatobiliary disorders	
Frequent	Elevated aspartate aminotransferase (AST) in serum, and elevated alanine aminotransferase (ALT) in serum*, hyperbilirubinaemia
Less frequent	Jaundice
Frequency unknown	Hepatic cholestasis, hepatic failure (see section 4.4)
Skin and subcutaneous tissue disorders	
Frequent:	Pruritus, rash
Frequency unknown:	Severe skin reactions, including Stevens-Johnson syndrome
General disorders and administration site conditions	
Frequent:	Headache, impaired healing, injection site reaction
Less frequent:	Injection site inflammation, injection site pain, injection site oedema, injection site phlebitis
Investigations	
Frequent:	Elevated amylase in serum, increased blood urea nitrogen (BUN)

*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.

Description of selected adverse reactions

Gastrointestinal adverse reactions

Discontinuation from tigecycline was most frequently associated with nausea and vomiting.

Antibiotic class effects

Pseudomembranous colitis which may range in severity from mild to life-threatening (see section 4.4).

Overgrowth of non-susceptible organisms, including fungi (see section 4.4).

Tetracycline class effects

Tigecycline as in TYCLIN is structurally similar to tetracycline class antibiotics. Tetracycline class adverse reactions may include photosensitivity, pseudotumor cerebri, pancreatitis and anti-anabolic action which has led to increased BUN, azotaemia, acidosis, and hyperphosphataemia (see section 4.4).

Tigecycline may be associated with permanent tooth discolouration if used during tooth development (see section 4.4).

Following a pooled analysis of all Phase 3 and 4 trials it was reported that death occurred in slightly more patients on tigecycline than in the comparator medicines.

Paediatric population

Adequate safety data are not available (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc-org) found on SAHPRA website.

4.9 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 healthy volunteers resulted in an increased incidence of nausea and vomiting. Tigecycline is not removed in significant quantities by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and Medium Spectrum Antibiotics

Pharmacotherapeutic group: Antibacterials for systemic use, tetracyclines, ATC code: J01AA12.

Mechanism of action

Tigecycline, a glycylcycline antibiotic structurally related to minocycline (a tetracycline), 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 is considered to be bacteriostatic.

Resistant organisms

Gram-negative aerobes

Pseudomonas aeruginosa

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 *Enterobacterales* 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 multi-drug 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 *Enterobacterales*. Decreased susceptibility in both groups has been attributed to the overexpression of the non-specific AcrAB multi-drug efflux pump. Decreased susceptibility in *Acinetobacter baumannii* has been attributed to the overexpression of the AdeABC efflux pump.

5.2 Pharmacokinetic properties

The mean pharmacokinetic parameters of tigecycline are summarised in the table below. Intravenous infusions of tigecycline should be administered over approximately 30 to 60 minutes.

Mean (CV %) pharmacokinetic parameters of tigecycline:

	Single Dose	Multiple Dose [c]

	100 mg	50 mg every 12 hours
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 marrow, salivary glands, thyroid gland, spleen, and kidney. In humans,

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

Two studies reported on the steady-state pharmacokinetic profile of tigecycline in specific tissues or fluids of healthy subjects receiving tigecycline 100 mg loading dose followed by six 50 mg doses every 12 hours. In a bronchoalveolar lavage study, samples were collected by standardised bronchoscopy at 2, 3, 4, 6, 12 and 24 hours after administration of the last dose. The tigecycline AUC_{0-12h} (134 µg·h/mL) in alveolar cells was 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 higher than the AUC_{0-12h} in serum. In a skin blister study, blood and blister samples were collected at 0,5, 1, 2, 3, 4, 6, 8, 12 and 24 hours after the last dose. The AUC_{0-12h} (1,61 µg·h/mL) of tigecycline in skin blister fluid was 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, lung and colon. The concentration of tigecycline in these tissues after multiple doses has not been studied.

Biotransformation

Tigecycline is not extensively metabolised. On average, it is estimated that less than 20 % of tigecycline is metabolised before excretion. *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 the 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.

Tigecycline is a substrate of P-gp based on an *in vitro* study using a cell line overexpressing P-gp. The potential contribution of P-gp-mediated transport to the in vivo disposition of tigecycline is not known.

Special populations

Hepatic impairment

The single-dose pharmacokinetic disposition of tigecycline was not altered in patients with mild hepatic impairment. However, systemic clearance of tigecycline was reduced and the half-life of tigecycline was prolonged in some patients with moderate hepatic impairment (Child Pugh B). In addition, systemic clearance of tigecycline was reduced and the half-life of tigecycline was prolonged 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).

Renal impairment

The single-dose pharmacokinetic disposition of tigecycline was not altered in patients with renal insufficiency (creatinine clearance <30 mL/min). No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing haemodialysis (see section 4.2).

Elderly

No overall differences in pharmacokinetics were observed between healthy elderly patients and younger patients receiving a single, 100 mg dose of tigecycline. Therefore, no dosage adjustment is necessary based on age (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

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

TYCLIN must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

36 months.

Reconstituted solution:

Once reconstituted with 0,9 % Sodium chloride injection, Dextrose 5 % or Ringer Lactate, TYCLIN powder for solution for infusion should be used immediately. If storage is necessary, both the reconstituted solution and diluted solution of TYCLIN are physically, chemically and microbially stable for at least 24 hours at room temperature (up to 6 hours in the vial and the remaining time in the intravenous bag) and for 48 hours at 2-8 °C following immediate transfer of the reconstituted solution into the intravenous bag.

6.4 Special precautions for storage

Store at or below 25 °C.

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

10-mL type I colourless glass vial with a 20-mm chlorobutyl rubber stopper and a 20-mm aluminium-plastic overseal.

TYCLIN is distributed as a single vial or 10-vial tray pack; not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Compatible intravenous solutions include 0,9 % Sodium Chloride Injection, 5 % Dextrose Injection and Lactated Ringer’s Injection.

TYCLIN is compatible with the following medicines or diluents when used with either 0,9 % Sodium chloride injection or 5 % Dextrose injection and administered simultaneously through the same line: amikacin, dobutamine, dopamine HCl, gentamicin, haloperidol, Lactated Ringer's, lidocaine HCl, metoclopramide, morphine, norepinephrine, piperacillin/tazobactam (EDTA formulation), potassium chloride, propofol, ranitidine HCl, theophylline, and tobramycin.

The lyophilised powder should be reconstituted with 5,3 mL of Sodium chloride 9 mg/mL (0,9 %) solution for injection, Dextrose 50 mg/mL (5 %) solution for 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 medicine 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). For a 100 mg dose, reconstitute using two vials into a 100 mL intravenous bag or other suitable infusion container (e.g., glass bottle). *Note:* The vial contains a 6 % overage. Thus, 5 mL of reconstituted solution is equivalent to 50 mg of the medicine.

The reconstituted solution should be yellow to orange in colour; if not, the solution should be discarded. Parenteral products should be inspected visually for particulate matter and discolouration (e.g., green or black) prior to administration. For storage conditions after reconstitution, see section 6.3.

TYCLIN should be administered intravenously through a dedicated line or through a Y-site. If the same intravenous line is used for sequential infusion of several active substances, the line should be flushed before and after infusion of tigecycline with either Sodium chloride 9 mg/mL (0,9 %) solution for injection or Dextrose 50 mg/mL (5 %) solution for injection. Injection should be made with

an infusion solution compatible with TYCLIN and with any other medicine(s) administered via this common line (see section 6.2).

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

59/20.1.1/0424.423

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 April 2026

10. DATE OF REVISION OF THE TEXT

Not applicable.