PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TIZEG

50 mg tigecycline powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL vial contains 50 mg of tigecycline. After reconstitution,

1 mL of solution for intravenous injection contains 10 mg of tigecycline.

Sugar free.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for infusion

TIZEG is a light yellowish orange lyophilised cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- Complicated skin and skin structure 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, Escherischia 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 **TIZEG** is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous (IV) infusions of **TIZEG** should be administered over approximately 30 to 60 minutes every 12 hours.

The recommended duration of treatment with **TIZEG** 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.

Use in patients with renal impairment

No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing haemodialysis. (See **section 5.2**, Renal insufficiency).

Use in patients with 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 **TIZEG** 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**, Hepatic insufficiency.)

Use in elderly

No dosage adjustment is necessary in elderly patients. (See **section 4.4,** Elderly Use).

Race and gender

No dosage adjustment is necessary based on race or gender. (See **section 5.2**).

Paediatric Population

Safety and effectiveness in patients under 18 years of age have not been reported. Therefore, use in patients under 18 years of age is not recommended. (See **section 4.4**).

Method of administration

Tigecycline is to be administered only by intravenous infusion.

For instructions on reconstitution and dilution of the medicine before administration, see **section 6.6**

4.3 Contraindications

- Hypersensitivity to the active substance tigecycline or to any of the excipients listed in section 6.1.
- Pregnancy and Lactation

4.4 Special warnings and precautions for use

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 been reported 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.

Superinfection

In reported 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 therapy consideration should be given to instituting alternative antibacterial therapy that has been reported 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 (see **sections 4.3 and 4.8**).

Hepatic failure

Cases of liver injury with a predominantly cholestatic pattern have
been reported in patients receiving tigecycline treatment, 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 should be considered (see **section 4.8**).

Tetracycline class antibiotics

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. TIZEG may have adverse reactions similar to tetracycline class antibiotics. Such reactions may include photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic action which has led to increased BUN (blood urea nitrogen), azotaemia, acidosis, and hyperphosphataemia (see **section 4.8**). Therefore, TIZEG should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics.

Pancreatitis

Acute pancreatitis, which can be serious, has been reported (frequency: less frequent) in association with **TIZEG** 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. 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 improve after tigecycline discontinuation. Consideration should be given to the cessation of treatment with tigecycline in cases suspected of having developed pancreatitis.

Coagulopathy

TIZEG 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 **TIZEG** 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 **TIZEG** 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 disease, such as those that were immunocompromised, patients with decubitus ulcer infections, or patients that had infections requiring longer than 14 days of treatment (for example, necrotizing fasciitis), were not enrolled. A limited number of patients were enrolled with co-morbid factors such as diabetes, peripheral vascular disease, intravenous substance abuse, and 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 in a large study in patients with diabetic foot infection, reported that tigecycline was less effective than comparator, therefore, tigecycline 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 **TIZEG** 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 may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy (see section 4.8).

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

The safety and efficacy of **TIZEG** in patients with hospital acquired pneumonia have not been reported. In a study of patients with hospital acquired pneumonia, patients were randomized 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 reported lower cure rates (47,9 % versus 70,1 % for the clinically evaluable population) and greater mortality (19,1 % versus 11,5 %) than the comparator.

Paediatric population

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.

Nausea and vomiting are very common adverse reactions in children and adolescents (see **section 4.8**). Attention should be paid to possible dehydration. Tigecycline should be preferably administered over a 60-minute length of infusion in paediatric patients.

Abdominal pain is commonly reported in children as it is in adults. Abdominal pain may be indicative of pancreatitis. If pancreatitis develops, treatment with tigecycline should be discontinued.

Liver function tests, coagulation parameters, haematology parameters, amylase and lipase should be monitored prior to treatment initiation with tigecycline and regularly while on treatment.

Elderly Use

Reported clinical studies included elderly subjects 65 years and over and no unexpected overall differences in safety or effectiveness were reported between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

Abuse and Dependence

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

Excipient information

This medicine contains 71,77 mg sodium per 5 mL of reconstituted solution for infusion, equivalent to 3,6 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

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

In vitro studies in human liver microsomes reported that tigecycline does not inhibit metabolism mediated by any of the following 6 cytochrome CYP450 isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. Therefore, **TIZEG** is not expected to alter the metabolism of medicines metabolized by these enzymes. 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 mg daily) when administered in healthy adults. Tigecycline slightly decreased the Cmax 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.

Digoxin did not affect the pharmacokinetic profile of tigecycline. Therefore, no dosage adjustment is necessary when **TIZEG** is administered with digoxin.

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

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

Concomitant use of tigecycline and calcineurin inhibitors such as tacrolimus or cyclosporine may lead to an increase in serum trough concentrations of the calcineurin inhibitors. Therefore, serum concentrations of the calcineurin inhibitor should be monitored during treatment with tigecycline to avoid drug toxicity.

Based on a reported *in vitro* study 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.

Interference with Laboratory and Other Diagnostic Tests

There are no reported drug-laboratory test interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

TIZEG may cause foetal harm when administered to a pregnant woman. Results of animal studies reported that tigecycline crosses the placenta and is found in foetal tissues. There are no reported studies of **TIZEG** in pregnant women.

TIZEG should not be used during pregnancy (See **section 4.3)**. **TIZEG** has not been studied for use during labour and delivery.

Breast-feeding

It is unknown whether tigecycline/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have reported excretion of tigecycline/metabolites in milk. A risk to the newborns/infants cannot be excluded.

Fertility

The effects of tigecycline on fertility in humans have not been studied. Tigecycline reported to not affect mating or fertility in rats. In female rats, no compound-related effects on ovaries or oestrus cycles were reported at exposures up to 4,7 times the human daily dose based on AUC.

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

In clinical trials, the most frequent medicine-related treatment emergent adverse reactions reported 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, including clinical trials and post-marketing experience, are tabulated below.

Tabulated list of adverse reactions

System Organ Class	***Frequent***	***Less frequent***	***Frequency not known (cannot be estimated from the reported 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), hypofibrinogenaemia	
Immune system disorders			anaphylaxis/ anaphylactoid reactions* (see **sections 4.3 and 4.4**)
Metabolism and nutrition disorders	hypoglycaemia, bilirubinaemia	hypoproteinaemia	
Nervous system disorders	dizziness		
Vascular disorders	phlebitis	thrombophlebitis	

Gastrointestinal disorders	nausea, vomiting, diarrhea, abdominal pain, dyspepsia, anorexia	acute pancreatitis (see **section 4.4**)	
Hepatobiliary disorders	elevated aspartate aminotransferase (AST) in serum, and elevated alanine aminotransferase (ALT) in serum, hyperbilirubinaemia	jaundice, liver injury, mostly cholestatic	hepatic failure* (see **section 4.4**), hepatic cholestasis
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 reaction, 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 (see **section 4.4**).

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

Tetracycline class effects

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. Tetracycline class adverse reactions may include photosensitivity, pseudotumour 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**).

Table: Patients with Adverse events with outcome of death by Infection type

	Tigecycline	**Comparator**	**Risk Difference***
Infection Type	%	%	% (95 % CI)
cSSSI	1,1	0,2	0,9 (-0,3; 2,2)
cIAI	2,9	2,1	0,9 (-0,8; 2,6)
CAP	2,8	2,6	0,2 (-2,3; 2,7)
HAP	13,9	12,0	1,9 (-2,6; 6,4)
Non-VAP[a]	11,9	12,2	-0,3 (-5,4; 4,9)
VAP[a]	19,1	11,5	7,6 (-2,0; 16,9)

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI = Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia

*The difference between the percentage of patients who died in tigecycline and comparator treatment groups.

[a] These are the subgroups of the HAP population

The frequent drug-related treatment emergent events reported in patients treated with **TIZEG** were nausea 20,4 (12,9 % mild; 6,6 % moderate; 0,8 % Severe) and vomiting 13,5 % (8,3 % mild; 4,5 % moderate; 0,6 % severe). In general, nausea or vomiting occurred early (days 1 - 2).

Discontinuation from **TIZEG** was most frequently associated with nausea (1, 3 %) and vomiting (1,0 %).

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. Health care providers are asked to report any suspected adverse 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 **TIZEG** at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. **TIZEG** is not removed in significant quantities by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

Category A 20.1.1 Broad and Medium Spectrum Antibiotics

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

PHARMACOLOGICAL ACTION

Mode of Action

Tigecycline, a glycylcycline antibiotic, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. Tigecycline is considered to be bacteriostatic.

5.2 Pharmacokinetic properties

The mean pharmacokinetic parameters of tigecycline are summarized in table below.

Intravenous infusions of tigecycline should be administered over approximately 30 to 60 minutes.

Table: Mean (CV %) Pharmacokinetic Parameters of Tigecycline

	Single Dose 100 mg	**Multiple Dose [c]** 50 mg q12 h
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 reported in clinical studies (0,1 to 1,0 µg/mL). Animal and human pharmacokinetic studies have reported that tigecycline readily distributes to tissues. In rats receiving single or multiple doses of 14C-tigecycline, radioactivity was well distributed to most tissues, with highest overall exposure reported 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 that tigecycline is extensively distributed beyond the plasma volume and concentrates into tissues of humans.

Two studies reported 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 reported bronchoalveolar lavage study, the tigecycline AUC_{0-12h} (134 µg*h/mL) in alveolar cells was approximately 77,5-fold higher than the AUC_{0-12h} in the serum of these subjects, and the AUC_{0-12h} (2,28 µg*hr/mL) in the epithelial lining fluid was approximately 32 % higher than the AUC_{0-12h} in serum. In a reported skin blister study, the AUC_{0-12h} (1,61 µg*h/mL) of tigecycline in skin blister fluid was approximately 26 % lower than the AUC_{0-12h} in the serum of these subjects.

In a reported 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 in tissues versus serum in gallbladder (38-fold), lung (8,6-fold), and colon (2,1-fold). The concentration of tigecycline in these tissues after multiple doses has not been reported.

Metabolism

Tigecycline is not extensively metabolized. Reported *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 14C-tigecycline, tigecycline was the primary 14C-labeled material recovered in urine and feces, but a glucuronide, an N-acetyl metabolite, and a tigecycline epimer (each at no more than 10 % of the administered dose) were also reported.

Elimination

The recovery of total radioactivity in feces and urine following administration 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 Populations

Hepatic Insufficiency

In a reported study comparing patients with mild hepatic impairment (Child Pugh A), patients with moderate hepatic impairment (Child Pugh B), and 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). 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 reported 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, Use in patients with hepatic impairment.)

Renal insufficiency

A reported single dose study compared subjects with severe renal impairment (creatinine clearance ≤ 30 mL/min), end stage renal disease (ESRD) patients receiving tigecycline 2 hours before haemodialysis, ESRD patients receiving tigecycline after haemodialysis, and healthy control subjects. The pharmacokinetic profile of tigecycline was not reported to be significantly 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**, Use in patients with renal impairment.)

Elderly

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

Gender

In a reported analysis of women and men participating in clinical pharmacology studies, there was no significant difference reported 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 reported analysis of Asian subjects, Black subjects, Hispanic subjects, White subjects, and subjects classified as “other” participating in clinical pharmacology studies, there was no significant difference reported 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.

Paediatric population

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sulphobutyl ether betacyclodextrin sodium

Hydrochloric acid

Water for injection

6.2 Incompatibilities

The following active substances should not be administered simultaneously through the same line as **TIZEG**: amphotericin B, amphoterecin B lipid complex, diazepam, esomeprazole, omeprazole and intravenous solutions that could result in an increase of pH above 7.

6.3 Shelf life

24 Months

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

6.4 Special precautions for storage

Store at temperatures not exceeding 25 °C. Protect from light.

Once reconstituted in the I.V. bag, **TIZEG** may be stored at room temperature (not to exceed 25 °C) for up to 24 hours (up to 6 hours in the vial and the remaining time in the IV bag). Alternatively, **TIZEG** mixed with 0,9 % Sodium Chloride Injection, USP, 5 % Dextrose Injection, USP, or Lactated Ringer's Injection USP may be stored refrigerated at 2 °C to 8 °C for up to 48 hours following immediate transfer of the reconstituted solution into the IV bag.
If the storage conditions exceed 25 °C after reconstitution, **TIZEG** should be used immediately.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

10 mL clear glass vial stoppered with slotted grey bromobutyl rubber stopper and sealed with an orange aluminum flip-off seal. One such vial will be packed in a plastic tray and such one tray packed in a monocarton along with leaflet.
Ten such labelled vials will be packed in a carton with separator along with a leaflet.

6.6 Special precautions for disposal and other handling

The lyophilised powder should be reconstituted with 5 mL of 0,9 % sodium chloride solution for injection, USP or 5 % Dextrose Injection, USP or Lactated Ringer's Solution to achieve a concentration of 10 mg/mL of **TIZEG.** The vial should be gently swirled until the drug dissolves. Thereafter, withdraw entire contents 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. 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 **TIZEG** may be stored at room temperature for up to 24 hours (up to 6 hours in the vial and the remaining time in the I.V. bag). Alternatively **TIZEG** mixed with 0,9 % Sodium Chloride Injection, USP or 5 % Dextrose Injection, USP, may be stored refrigerated at 2 °C – 8 °C for up to 48 hours following immediate transfer of the reconstituted solution into the I.V. bag.

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

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

TIZEG may be administered intravenously through a dedicated line through a Y-site. If the same intravenous line is used for sequential infusion of several medicines, the line should be flushed before and after infusion of **TIZEG** with either 0,9 % Sodium Chloride Injection, USP, or 5 % Dextrose Injection, USP. Injection should be made with an infusion solution compatible with **TIZEG** and with any other drug(s) administered via this common line.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd.

a Sun Pharma company

14 Lautre Road, Stormill Ext 1,

Roodepoort, 1724,

South Africa.

8. REGISTRATION NUMBERS

56/20.1.1/0531

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31 January 2025