PROFESSIONAL INFORMATION FOR TIGEJEX

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TIGEJEX Lyophilised powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL contains 50 mg tigecycline.

Contains sugar (lactose monohydrate, 100,00 mg)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilised powder for injection.

TIGEJEX is an orange coloured Lyophilised cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

The recommended duration of treatment with TIGEJEX 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

Use in patients with renal impairment

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

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 TIGEJEX in patients with severe hepatic impairment (Child Pugh C), the dose of TIGEJEX 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 TIGEJEX 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.

4.3 Contraindications

TIGEJEX is contraindicated for use:

- In patients who have known hypersensitivity to tigecycline or to any of the excipients of TIGEJEX (listed in section 6.1).
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

An increase in all-cause mortality has been observed across clinical trials in tigecycline as in TIGEJEX treated patients versus comparator-treated patients. In a pooled analysis of trials that included a comparator, death occurred in 4,0% of patients receiving tigecycline and 3,0 % of patients receiving comparator medicines resulting in an unadjusted risk difference of 0,9%. 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 % 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.

TIGEJEX should not be used in hospital associated pneumonia (HAP) or ventilator associated pneumonia (VAP). The safety and efficacy of TIGEJEX in patients with hospital acquired pneumonia (HAP) have not been established. In a study of patients with hospital acquired pneumonia, patients were randomised to receive tigecycline as in TIGEJEX (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 (VAP) who received tigecycline had lower cure rates (47,9 % versus 70,1 % for the clinically evaluable population) and higher mortality 19,1 % versus 12,3 % than the comparator. Of those patients with ventilator-associated pneumonia and bacteraemia at baseline, those who received TIGEJEX had greater mortality 50,0 % versus 7,7 % than the comparator.

Anaphylaxis

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

Tetracycline class antibiotics

TIGEJEX is structurally similar to tetracycline class antibiotics. Therefore, TIGEJEX should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics.

Underlying diseases

Experience in the use of tigecycline for treatment of infections in patients with severe underlying diseases is limited.

In clinical trials in cSSTI, the most common type of infection in tigecycline treated-

patients was cellulitis (58.6 %), followed by major abscesses (24.9 %). 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 (25.8 %), peripheral vascular disease (10.4 %), intravenous substance abuse (4.0 %), and HIV-positive infection (1.2 %). Limited experience is also available in treating patients with concurrent bacteraemia (3.4 %). Therefore, caution is advised when treating such patients. The results in a large study in patients with diabetic foot infection, showed that tigecycline was less effective than comparator, therefore, tigecycline is not recommended for use in these patients (see section 4.1).

In clinical trials in cIAI, the most common type of infection in tigecycline-treated patients was complicated appendicitis (50.3 %), followed by other diagnoses less commonly reported such as complicated cholecystitis (9.6 %), perforation of intestine (9.6 %), intra-abdominal abscess (8.7 %), gastric or duodenal ulcer perforation (8.3 %), peritonitis (6.2 %) and complicated diverticulitis (6.0 %). 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 (3.3 %), or with surgically apparent multiple intra-abdominal abscesses (11.4 %). Limited experience is also available in treating patients with concurrent bacteraemia (5.6 %). Therefore, caution is advised when treating such patients.

Consideration should be given to the use of combination antibacterial therapy whenever tigecycline 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).

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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.

Use of TIGEJEX 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.

Results of studies in rats with tigecycline have shown bone discolouration. TIGEJEX may be associated with permanent tooth discolouration in humans during tooth development.

Pseudomembranous colitis has been reported with tigecycline as in TIGEJEX. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of TIGEJEX.

Caution should be exercised when considering TIGEJEX monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation.

Hepatic failure

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

TIGEJEX is structurally similar to tetracycline class antibiotics and may have similar adverse effects. Such effects may include photosensitivity, pseudotumour cerebri, and anti-anabolic action (which has led to increased BUN, uraemia, acidosis, and hyperphosphataemia).

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Pancreatitis

Acute pancreatitis, which can be fatal, has occurred in association with tigecycline as in TIGEJEX treatment. The diagnosis of acute pancreatitis should be considered in patients taking TIGEJEX 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 improved after tigecycline discontinuation. Cessation of the treatment with TIGEJEX in case suspected of having developed pancreatitis is advised.

Coagulopathy

TIGEJEX 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 TIGEJEX and regularly while on treatment.
Special care is recommended in seriously ill patients and in patients also using anticoagulants (see section 4.5).

Superinfection

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 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.

Paediatric use

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

Use in elderly

No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects. No dosage adjustment is necessary In elderly patients.

Excipient information

This medicine contains less than 1 mmol sodium (23 mg) per 5mL of suspension, That is to say essentially ‘sodium-free’.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Tigecycline as in TIGEJEX (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 TIGEJEX is administered with digoxin.

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Concomitant administration of tigecycline as in TIGEJEX (100 mg followed by 50 mg every 12 12 hours) and warfarin (25 mg single dose) to healthy subjects decrease in clearance of R-warfarin and S-warfarin by 40% and 23%, and an resulted in a increase in AUC by 68 % and 29 %, respectively. Tigecycline did not significantly alter the effects of warfarin on increased international normalised ratio (INR). In addition, warfarin did not affect the pharmacokinetic profile of tigecycline. However, prothrombin time or other suitable anticoagulation test should be monitored if TIGEJEX is administered with warfarin.

In vitro studies in human liver microsomes indicate that tigecycline as in TIGEJEX does not inhibit metabolism mediated by any of the following 6 cytochrome CYP450 isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. Therefore, TIGEJEX is not expected to alter the metabolism of medicines metabolised by these enzymes. In addition, because TIGEJEX is not extensively metabolised, clearance of TIGEJEX is not expected to be affected by medicines that inhibit or induce the activity of these CYP450 isoforms.

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

Tigecycline as in TIGEJEX 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 TIGEJEX is not known. Coadministration of P-gp inhibitors (e.g., ketoconazole or ciclosporine) or P-gp inducers (e.g., rifampicin) could affect the pharmacokinetics of TIGEJEX.

Concurrent use of antibiotics with oral contraceptives may render oral

contraceptives less effective.

Concomitant use of TIGEJEX 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 TIGEJEX to avoid medicine toxicity.

Interference with laboratory and other diagnostic tests

There are no reported drug-laboratory test interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Breastfeeding

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

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).

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4.8 Undesirable effects

Summary of the safety profile

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

The most frequent treatment-emergent adverse reactions, in patients treated with tigecycline as in TIGEJEX were nausea and vomiting. In general, nausea or vomiting occurred early (days 1 - 2).

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

Table 2: Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Frequent	Sepsis/septic shock, abscess, infections
Blood and lymphatic system disorders	Frequent Less frequent	Prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time (PT), thrombocytopenia Increased international normalised ratio (INR), hypofibrinogenaemia
Immune system disorders	Frequency unknown	Anaphylaxis / anaphylactoid reactions
Metabolism and nutrition disorders	Frequent	Hypoproteinaemia, hypoglycaemia
Nervous system	Frequent	Dizziness

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disorders		
Vascular disorders	Frequent Less frequent	Phlebitis Thrombophlebitis
Respiratory, thoracic and mediastinal disorders	Frequent	Pneumonia
Gastrointestinal disorders	Frequent Less frequent	Nausea, vomiting, diarrhoea, anorexia, abdominal pain, dyspepsia Acute pancreatitis
Hepato-biliary disorders	Frequent Less frequent Frequency unknown	Elevated aspartate aminotransferase (AST) in serum, elevated alanine aminotransferase (ALT) in serum*, hyperbilirubinaemia Jaundice Hepatic cholestasis, hepatic failure
Skin and subcutaneous tissue disorders	Frequent Less frequent	Pruritus, rash Severe skin reactions, including Stevens-Johnson Syndrome
General disorders and administration site conditions	Frequent Less frequent	Headache, impaired healing, injection site reaction Injection site inflammation, injection site pain, injection site oedema, injection site phlebitis
Investigations	Frequent	Elevated amylase in serum,

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		increased blood urea nitrogen (BUN)
*AST and ALT abnormalities in TIGEJEX treated patients were reported more frequently in the posttherapy period than in those in comparator-treated patients, which occurred more often on therapy.		

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 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 overdose with TIGEJEX. Intravenous administration of TIGEJEX at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. TIGEJEX 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

ATC code: J01AA12

Pharmacotherapeutic group: Antibacterials for systemic use, tetracyclines

Mechanism of action

Tigecycline, a glycylcycline antibiotic, structurally related to the tetracycline, minocycline, 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.

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.

Resistant organisms

Gram-negative aerobes

Pseudomonas aeruginosa

5.2. Pharmacokinetic properties

The mean pharmacokinetic parameters of tigecycline are summarised in Table 1. Intravenous infusions of tigecycline should be administered over approximately 30 to 60 minutes.

Table 1. Mean (CV %) pharmacokinetic parameters of tigecycline

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	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 14C-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. No data are available on whether tigecycline can cross the blood-brain barrier in humans.

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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.

In vitro studies in human liver microsomes indicate that tigecycline does not inhibit metabolism mediated by any of the following 6 cytochrome P450 (CYP) isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4 by competitive inhibition. In addition, tigecycline did not show NADPH-dependency in the inhibition of CYP2C9, CYP2C19, CYP2D6 and CYP3A, suggesting the absence of mechanism-based inhibition of these CYP enzymes.

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.

The total clearance of tigecycline is 24 L/h after intravenous infusion. Renal clearance is approximately 13 % of total clearance. Tigecycline shows a polyexponential elimination from serum with a mean terminal elimination half-life after multiple doses of 42 hours although high interindividual variability exists.

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 drug interaction study described above (see section 4.5).

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. Co-administration of P-gp inhibitors (e.g., ketoconazole or cyclosporine) or P-gp inducers (e.g., rifampicin) could affect the pharmacokinetics of tigecycline.

Special populations

Hepatic insufficiency:

In a 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 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).

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Renal insufficiency:

A single-dose study compared subjects with severe renal impairment (creatinine clearance CrCl ≤ 30 mL/min), 4 end stage renal disease patients receiving tigecycline 2 hours before haemodialysis, end stage renal disease patients receiving tigecycline after haemodialysis, and healthy control subjects. The pharmacokinetic profile of tigecycline was not altered in any of the renally impaired patient groups, nor was 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).

Elderly:

No overall differences in pharmacokinetics were observed between healthy elderly subjects and younger subjects 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 (used to adjust pH)

Sodium hydroxide (used to adjust pH)

6.2 Incompatibilities

The following medicines should not be administered simultaneously through the same line as TIGEJEX: amphotericin B, amphotericin B lipid complex, diazepam, esomeprazole and omeprazole.

6.3 Shelf life

24 months

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After reconstitution:

Once reconstituted in the IV bag, TIGEJEX may be stored for up to 24 hours (up to 6 hours in the vial and the remaining time in the IV bag).

Alternatively, TIGEJEX mixed with 0,9 % Sodium Chloride Injection or 5 % Dextrose Injection, may be stored for up to 45 hours following immediate transfer of the reconstituted solution into the IV bag.

6.4 Special precautions for storage

TIGEJEX should be stored at or below 25 °C prior to reconstitution.

Once reconstituted in the IV bag, TIGEJEX may be stored at room temperature (not to exceed 25 °C). Alternatively, TIGEJEX mixed with 0,9 % Sodium Chloride Injection or 5 % Dextrose Injection, may be stored refrigerated at 2 °C to 8 °C.

For storage conditions after reconstitution, see section 6.3.

6.5 Nature and contents of container

5 ml clear glass tubular vial with 13 mm slotted grey bromobutyl sterile rubber stopper (RFU) and sealed with 13 mm flip-off seal glossy green packed in a printed unit carton along with pack insert.

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.

The lyophilised powder should be reconstituted with 5 mL of 0,9 % Sodium Chloride Injection, or 5 % Dextrose Injection or Lactated Ringer’s Injection to achieve a concentration of 10 mg/mL of TIGEJEX. 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 (IV) 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 medicine products should be inspected visually for particulate matter and discolouration (e.g., green or black) prior to administration whenever solution and container permit.

TIGEJEX 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 TIGEJEX with either 0,9 % Sodium Chloride Injection, or 5 % Dextrose Injection. Injection should be made with an infusion solution compatible with TIGEJEX and with any other medicine(s) administered via this common line.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Lamar International (Pty) Ltd

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8. REGISTRATION NUMBERS

58/20.1.1/0015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

PROFESSIONAL INFORMATION FOR TIGEJEX

Registration date: 09 June 2026