SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Tigecycline Adco, 50 mg, (sterile powder for solution for intravenous infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg tigecycline. After reconstitution, 1 ml contains 10 mg of tigecycline.
Tigecycline Adco is sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile powder for solution for intravenous infusion.

Tigecycline Adco is a lyophilised orange to orange-red cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tigecycline Adco 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 Tigecycline Adco is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous (IV) infusions of Tigecycline Adco should be administered over approximately 30 to 60 minutes every 12 hours.

The recommended duration of treatment with Tigecycline Adco 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

Renal impairment

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

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

Elderly population

No dosage adjustment is necessary in elderly patients (see section 4.4 and 4.8).

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 established. Therefore, use in patients under 18 years of age is not recommended (see section 4.4).

Method of administration

Tigecycline Adco is administered only by intravenous infusion over 30 to 60 minutes (see sections 4.4 and 6.6).

For instructions on reconstitution & dilution of Tigecycline Adco before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to 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 (e.g. Tigecycline Adco) treated patients has 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.

Superinfection

From the studies conducted, 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 Adco therapy consideration should be given to instituting alternative antibacterial therapy that has been demonstrated to be efficacious in the treatment of the specific type of infection(s) present.

Anaphylaxis

Anaphylaxis/anaphylactoid reactions, potentially life-threatening, have been reported with tigecycline (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 Adco due to the underlying conditions or concomitant medicines, a possible contribution of Tigecycline Adco should be considered (see section 4.8).

Tetracycline class antibiotics

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. Tigecycline Adco 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, Tigecycline Adco should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics.

Pancreatitis

Acute pancreatitis, which can be serious, has occurred (frequency: less frequent) in association with Tigecycline Adco treatment (see section 4.8). The diagnosis of acute pancreatitis should be considered in patients taking Tigecycline Adco 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 Adco discontinuation. Consideration should be given to the cessation of treatment with Tigecycline Adco in cases suspected of having developed pancreatitis.

Underlying diseases

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

Consideration should be given to the use of combination antibacterial therapy whenever Tigecycline Adco 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.

Prothrombin time or other suitable anticoagulation test should be used to monitor patients if Tigecycline Adco is administered with anticoagulants (see section 4.5).

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 Adco may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken (see section 4.8).

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

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

Paediatric population
Safety and effectiveness in patients under 18 years of age have not been established. Therefore, use of Tigecycline Adco in patients under 18 years of age is not recommended.

4.5 Interaction with other medicines and other forms of interaction
Concomitant administration of tigecycline (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single dose) to healthy subjects resulted in a decrease in clearance of R-warfarin and S-warfarin by 40 % and 23 %, and an increase in AUC by 68 % and 29 %, respectively. 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 Tigecycline Adco is administered with warfarin.

Tigecycline Adco is not extensively metabolised. Therefore, clearance of Tigecycline Adco 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 (see section 5.2).

Tigecycline (100 mg followed by 50 mg every 12 hours) and digoxin (0,5 mg followed by 0,25 mg every 24 hours) were co-administered to healthy subjects in a medicine interaction study. Tigecycline slightly decreased the C_{max} of digoxin by 13 % but did not affect the AUC or clearance of digoxin. This small change in C_{max} did not affect the steady-state pharmacodynamic effects of digoxin as measured by changes in ECG intervals. In addition, digoxin did not affect the pharmacokinetic profile of tigecycline. Therefore, no dosage adjustment is necessary when Tigecycline Adco administered with digoxin.

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

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

Based on an *in vitro* study tigecycline is a P-gp substrate. Co-administration of P-gp inhibitors (e.g., ketoconazole or ciclosporin) or P-gp inducers (e.g., rifampicin) could affect the pharmacokinetics of tigecycline (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of Tigecycline Adco in pregnant women. Tigecycline Adco may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity.

Tigecycline Adco is contraindicated during pregnancy.

Breastfeeding

It is unknown whether tigecycline/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of tigecycline/metabolites in milk.

Tigecycline Adco is contraindicated during breastfeeding.

Fertility

Tigecycline did not affect mating or fertility in rats at exposures up to 4,7 times the human daily dose based on AUC. In female rats, there were no compound-related effects on ovaries or oestrus cycles at exposures up to 4,7 times the human daily dose based on AUC.

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	Frequent	Less frequent	Frequency unknown
Infections and infestations	Sepsis/septic shock, abscess, infections		
Respiratory, thoracic and mediastinal disorders	Pneumonia		
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, hypoproteinaemia		
Nervous system disorders	Dizziness		
Cardiac disorders	Phlebitis	Thrombophlebitis	
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, anorexia	Acute pancreatitis (see section 4.4)	
Hepato-biliary 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 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 Adco may be associated with permanent tooth discolouration if used during tooth development (see section 4.4).

Paediatric population

Very limited safety data were available from two PK studies (see section 5.2). No new or unexpected safety concerns were observed with tigecycline in these studies.

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 asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

No specific information is available on the treatment of overdosage with Tigecycline Adco. Intravenous administration of Tigecycline Adco at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. Tigecycline Adco 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, 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 *Enterobacteriaceae* due to multidrug resistance (MDR) efflux pumps has been shown. There is no target-based cross-resistance between tigecycline and most classes of antibiotics.

5.2 Pharmacokinetic properties

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

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

	Single Dose 100 mg	**Multiple Dose[c] 50 mg q12h**
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^{0-24} (µg·h/ml)	-	4,70 (36 %)
C_{min} (µg/ml)	-	0,13 (59 %)
$t_{1/2}$ (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 mcg/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 concentrates into tissues of humans.

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

In clinical pharmacology studies using the therapeutic dosage regimen of 100 mg followed by 50 mg q12h, serum tigecycline steady-state C_{max} was 866±233 ng/ml for 30-minute infusions and 634±97 ng/ml for 60-minute infusions. The steady-state AUC_{0-12h} was 2 349±850 ng•h/ml.

Biotransformation

On average, it is estimated that less than 20 % of tigecycline is metabolised before excretion. In healthy male volunteers, following the administration of ^{14}C-tigecycline, unchanged tigecycline was the primary ^{14}C-labelled material recovered in urine and faeces, but a glucuronide, an N-acetyl metabolite and a tigecycline epimer 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 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.

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.

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 by 25 %, and the half-life of tigecycline was prolonged by 23 % in patients with moderate or severe hepatic impairment (Child Pugh B and C), respectively (see section 4.2).

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 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, n=6). In severe renal impairment, AUC was 30 % higher than in subjects with normal renal function (see section 4.2). 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 (see section 4.2).

Gender

Studies performed indicate no clinically relevant differences in the clearance of tigecycline between men and women. Therefore, no dosage adjustment is necessary based on gender.

Race

There were no differences in the clearance of tigecycline based on race. Therefore, no dosage adjustment necessary based on race.

Weight

Clearance, weight-normalised clearance, and AUC were not appreciably different among patients with different body weights, including those weighing ≥ 125 kg. AUC was 24 % lower in patients weighing ≥ 125 kg. No data is available for patients weighing 140 kg and more.

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

L-arginine
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 Adco: Amphotericin B, amphotericin B lipid complex, diazepam,

esomeprazole, omeprazole and intravenous solutions that could result in an increase of pH above 7.

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

6.3 Shelf life

2 years.

Reconstituted solution:

Once reconstituted Tigecycline Adco 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, Tigecycline Adco 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.

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

Tigecycline Adco is packaged in a 5 ml Type 1 clear glass vials fitted with grey butyl rubber stoppers and aluminium flip-off seal with a top orange plastic cap, packed inside a cardboard carton with a leaflet.

Pack size: 1 or 10 vials per carton.

6.6 Special precautions for disposal and other handling

The lyophilised powder should be reconstituted with 5,3 ml of 0,9 % Sodium Chloride Injection, USP, or 5 % Dextrose Injection, USP or Lactated Ringer's Solution to achieve a concentration of 10 mg/mL of Tigecycline Adco. 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 IV bag for infusion. For a 100 mg dose, reconstitute using two vials into a 100 ml IV bag. (Note: The vial contains a 6 % overage. Thus, 5 ml of reconstituted solution is equivalent to 50 mg of the medicine). The reconstituted solution should be yellow to orange in colour; if not, the solution should be discarded. Parenteral medicines should be inspected visually for particulate matter and discolouration (e.g., green or black) prior to administration whenever solution and container permit. Once reconstituted Tigecycline Adco 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, Tigecycline Adco 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

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

Compatible intravenous solutions include sodium chloride 9 mg/ml (0,9 %) solution for injection, dextrose 50 mg/ml (5 %) solution for injection, and Lactated Ringer's solution for injection.

Tigecycline Adco 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.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand
1685
South Africa

8. REGISTRATION NUMBER(S)

55/20.1.1/0750

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 09 May 2023

10. DATE OF REVISION OF THE TEXT

Date of approval: 09 May 2023