PROFESSIONAL INFORMATION

CYTAGIL IV

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CYTAGIL IV powder for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml vial contains 50 mg tigecycline.

When reconstituted as directed, each 1 mL contains 10 mg tigecycline.

Sugar and sodium free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

An orange lyophilised powder.

The reconstituted solution is orange in colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CYTAGIL IV 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, 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 uniforms, Bacteroides vulgatus, Clostridium perfringens* and *Peptostreptococcus micros.*

4.2 Posology and method of administration

Posology

The recommended dosage regimen for CYTAGIL IV is an initial dose of 100 mg, followed by 50 mg every 12 hours.

Intravenous (IV) infusions of CYTAGIL IV should be administered over approximately 30 to 60 minutes every 12 hours.

The recommended duration of treatment with CYTAGIL IV 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 CYTAGIL IV is necessary in patients with renal impairment or in patients undergoing haemodialysis (see section 5.2).

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

Use in elderly

No dosage adjustment is necessary in elderly patients (see section 5.2).

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

Intravenous infusion.

CYTAGIL IV must be reconstituted, transferred and further diluted for I.V. infusion. For instructions on reconstitution & dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- hypersensitivity to tigecycline or to any of the ingredients of CYTAGIL IV (see section 6.1).
- pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Superinfection

Use of CYTAGIL IV may result in overgrowth of non-susceptible organisms, including fungi. Patients, especially those developing impaired healing (e.g. of a surgical wound), should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.
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 skin and soft tissue infection (cSSTI) or complicated intra-abdominal infections (cIAI) is identified after initiation of CYTAGIL IV 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 have been reported with nearly all antibacterial medicines, including CYTAGIL IV, and may be life-threatening.

Hepatic failure

Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline.
Although hepatic failure may occur in patients treated with CYTAGIL IV due to the underlying conditions or concomitant medicinal products, a possible contribution of CYTAGIL IV should be considered (see section 4.8).

Tetracycline class antibiotics

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics, such as CYTAGIL IV, and may have similar side effects. Such effects may include photosensitivity, pseudotumour cerebri, and anti-anabolic action (which has led to increased blood urea nitrogen (BUN), azotaemia,

acidosis, and hyperphosphataemia). Therefore CYTAGIL IV should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics.

Pancreatitis

As with tetracycline, pancreatitis has been reported with the use of CYTAGIL IV.

The diagnosis of acute pancreatitis should be considered in patients taking CYTAGIL IV who develop clinical symptoms, signs, or laboratory abnormalities suggestive of acute pancreatitis. Most cases of pancreatitis develop after at least one week of treatment and can also develop without known risk factors for pancreatitis. Patients usually improve after CYTAGIL IV discontinuation. Consideration should be given to the cessation of treatment with CYTAGIL IV in patients suspected of having developed pancreatitis.

Coagulopathy

Tigecycline may prolong both prothrombin time (PT) and activated partial thromboplastin time (aPTT). Additionally, hypofibrinogenaemia has been reported with the use of tigecycline, as in CYTAGIL IV. Therefore, blood coagulation parameters such as PT or other suitable anticoagulation test, including blood fibrinogen, should be monitored prior to treatment initiation with CYTAGIL IV 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

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

Caution is advised when treating patients with underlying conditions such as diabetes, peripheral vascular disease, intravenous substance abuse, HIV-positive infection, concurrent bacteraemia, patients with APACHE II scores > 15, surgically apparent multiple intra-abdominal abscesses and

immunocompromised patients.

Consideration should be given to the use of combination antibacterial therapy whenever CYTAGIL IV is to be administered to severely ill patients with complicated intra-abdoninal infections (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, as in CYTAGIL IV 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

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

Intra-abdominal infections

Caution should be exercised when considering CYTAGIL IV monotherapy in patients with cIAI3ecx secondary to clinically apparent intestinal perforation. Intestinal perforations and sepsis/septic shock have been reported in this patient group, however the relationship of this outcome to CYTAGIL IV treatment has not been established.

Hospital acquired pneumonia

The safety and efficacy of CYTAGIL IV in patients with hospital acquired pneumonia have not been established.

Tooth discolouration

CYTAGIL IV may be associated with permanent tooth discolouration during tooth development.

Abuse and dependence

Medicine abuse and dependence have not been demonstrated and are unlikely.

Elderly patients

No unexpected overall differences in safety or effectiveness have been observed between older patients (> 65 years old) and younger patients, however greater sensitivity to side effects by some elderly patients cannot be ruled out.

Paediatric population

Safety and effectiveness in patients under 18 years of age have not been established. Therefore, use of CYTAGIL IV in patients under 18 years of age is not recommended.

4.5 Interaction with other medicines and other forms of interaction

Calcineurin inhibitors

Concomitant use of CYTAGIL IV 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 CYTAGIL IV to avoid medicine toxicity.

Warfarin

Concomitant administration of CYTAGIL IV **(**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.
CYTAGIL IV does not significantly alter the effects of warfarin on increased international normalized ratio (INR). In addition, warfarin does not affect the pharmacokinetic profile of CYTAGIL IV. However, prothrombin time or other suitable anticoagulation test should be monitored if CYTAGIL IV is

administered with warfarin.

Oral contraceptives

Concurrent use of antibiotics, such as CYTAGIL IV, with oral contraceptives may render oral contraceptives less effective. Patients should be advised to use additional contraception during treatment with CYTAGIL IV.

Digoxin

CYTAGIL IV (100 mg followed by 50 mg every 12 hours) decreases the C_{max} of digoxin (0,5 mg followed by 0,25 mg every 24 hours) were co-administered to healthy subjects in a drug interaction study. CYTAGIL IV 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} does not affect the steady-state pharmacodynamic effects of digoxin as measured by changes in ECG intervals. In addition, digoxin does not affect the pharmacokinetic profile of CYTAGIL IV. Therefore, no dosage adjustment is necessary when CYTAGIL IV is administered with digoxin.

CYP450 isoforms

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

Antibiotic medicines

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

P-gp inhibitors and inducers

Based on an *in vitro* study tigecycline, as in CYTAGIL IV, 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 CYTAGIL IV.

Interference with laboratory and other diagnostic tests

There are no reported medicine-laboratory test interactions.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Women of childbearing potential should ensure effective contraception.

For maximal protection, use of additional non-hormonal contraception (e.g. barrier contraceptives) is recommended during treatment and also for some time after the treatment is stopped.

Pregnancy

CYTAGIL IV may cause foetal harm when administered to a pregnant woman. Results of animal studies indicate that CYTAGIL IV crosses the placenta and is found in foetal tissues. There are no adequate and well-controlled studies of CYTAGIL IV in pregnant women, nor its use during labour and delivery.

Breastfeeding

Results from animal studies using ^{14}C-labeled tigecycline, as in CYTAGIL IV, indicate that CYTAGIL IV

is excreted readily via the milk of lactating rats. It is not known whether tigecycline is excreted in human milk.

CYTAGIL IV should therefore not be used during pregnancy or lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

CYTAGIL IV can cause dizziness which may impair the ability to drive and/or operate machinery.

4.8 Undesirable effects

a) Summary of the safety profile

Studies indicate that the most common adverse reactions, nausea and vomiting, occur in early treatment (days 1 and 2), are reversible and mild or moderate in severity.

b) Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Frequent	Sepsis/septic shock, abscess, infections
Respiratory, thoracic and mediastinal disorders	Frequent	Pneumonia

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	Bilirubinaemia, hypoproteinaemia, hypoglycaemia
Nervous system disorders	Frequent	Dizziness
Vascular disorders	Frequent Less frequent	Phlebitis Thrombophlebitis
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Nausea, vomiting, diarrhoea, anorexia, abdominal pain, dyspepsia Acute pancreatitis Pseudomembranous colitis, tooth discolouration of developing teeth

Hepato-biliary disorders	Frequent Less frequent Frequency unknown	Elevated aspartate aminotransferase (AST) in serum, elevated alanine aminotransferase (ALT) in serum, hyperbilirubinaemia Jaundice, liver injury, mostly cholestatic Hepatic cholestasis, hepatic failure
Skin and subcutaneous tissue disorders	Frequent Frequency unknown	Pruritus, rash Severe skin reactions including Stevens-Johnson Syndrome
General disorders and administrative site conditions	Frequent Less frequent	Headache, injection site reaction, impaired healing Injection site inflammation, injection site pain, injection site oedema, injection site phlebitis
Investigations	Frequent	Elevated amylase in serum, increased blood urea nitrogen (BUN)

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms

No specific information is available on the treatment of overdosage with CYTAGIL IV. Intravenous administration of CYTAGIL IV at a single dose of 300 mg over 60 minutes results in an increased incidence of nausea and vomiting.

Management of overdose

CYTAGIL IV is not removed in significant quantities by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, tetracyclines

ATC code: J01AA12

Pharmacological classification: A 20.1.1 Broad and Medium Spectrum Antibiotics

Mechanism of action

Tigecycline, a glycylcycline antibiotic, inhibits protein translation in bacteria by binding to 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.

Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications. The information below provides only approximate guidance on the probability as to whether the

microorganism will be susceptible to tigecycline or not:

Mechanism of resistance

Tigecycline is able to overcome the two major tetracycline resistance mechanisms, ribosomal protection and efflux. Cross-resistance between tigecycline and minocycline-resistant isolates among the*Enterobacteriaceae* due to multi-drug resistance (MDR) efflux pumps has been shown. There is no target-based cross-resistance between tigecycline and most classes of antibiotics.

Tigecycline is vulnerable to chromosomally-encoded 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 *Enterobacteriaceae*.

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 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_{0-24h} (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 (0,1 to 1,0 µg/mL). Pharmacokinetic studies have demonstrated that tigecycline readily distributes to tissues. The steady-state volume of distribution of tigecycline averages 500 to 700 L (7 to 9 L/kg), indicating tigecycline is extensively distributed beyond the plasma volume and into the tissues of humans.

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 subjects 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 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.

Pharmacokinetics in special patient groups

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 23 age- and weight-matched healthy control subjects ,the single-dose pharmacokinetic disposition of tigecycline is not altered in patients with mild hepatic impairment (Child Pugh A). However, systemic clearance of tigecycline is reduced by 25 %, and the half-life of tigecycline is prolonged by 23 % in patients with moderate hepatic impairment (Child Pugh B). In addition, systemic clearance of tigecycline is reduced by 55 %, and the half-life of tigecycline 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).

Renal insufficiency

The pharmacokinetic profile of tigecycline is not altered in renally impaired patients, nor is 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 are observed between elderly (age > 75 years) and younger patients receiving 100 mg tigecycline, therefore, no dosage adjustment is necessary based on age.

Gender

No dosage adjustment is necessary based on gender.

Race

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

Arginine

Hydrochloric acid (for pH-adjustment)

6.2 Incompatibilities

The following medicines should not be administered simultaneously through the same line as CYTAGIL IV: amphotericin B, amphoterecin B lipid complex, diazepam, esomeprazole, omeprazole, or intravenous solutions that could result in an increase of pH above 7.

CYTAGIL IV must not be mixed with any other medicines except those mentioned in section 6.6.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ˚C prior to reconstitution. The product should be used immediately after reconstitution. The reconstituted product can be stored up to 1 hour at 25 ˚C in the vial or IV bag or bottle if required.

6.5 Nature and contents of container

CYTAGIL IV is packed into a 10 ml Type I glass vial, fitted with a grey chromobutyl stopper, aluminium cap and white flip-off cap. 10 vials are supplied in an outer carton.

6.6 Special precautions for disposal and other handling

Reconstitution

The lyophilised powder should be reconstituted with 5,3 mL of either 0,9 % sodium chloride intravenous infusion, dextrose (5 %) intravenous infusion or Ringer's lactate intravenous infusions, to achieve a concentration of 10 mg/mL of CYTAGIL IV.

The vial should be gently swirled until the powder 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 infusion bottle.

For a 100 mg dose, reconstitute using two vials into a 100 mL intravenous bag for infusion or infusion bottle.

The reconstituted solution should be orange in colour and free from visible particles; 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 whenever solution and container permit.

CYTAGIL IV 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 CYTAGIL IV with sodium chloride (0,9 %), dextrose (5%) or ringer lactate intravenous infusions.

Injection should be made with an infusion solution compatible with CYTAGIL IV and with any other medicine(s) administered via this common line (see section 6.2).

Compatible solutions

Compatible intravenous solutions include sodium chloride (0,9 %), dextrose (5 %) and Ringer's lactate intravenous infusions.

Compatible medicines and diluents

CYTAGIL IV is compatible with the following medicines or diluents when used with either sodium chloride (0,9 %), dextrose (5 %) and Ringer's lactate intravenous infusions and administered simultaneously through the same line: amikacin, dobutamine, dopamine HCl, gentamycin, haloperidol, Ringer's lactate, lidocaine HCl, morphine, noradrenaline (norepinephrine), piperacillin/tazobactam (EDTA formulation) potassium chloride, propofol, ranitidine HCl, theophylline and tobramycin.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

A53/20.1.1/0715

9. DATE OF FIRST AUTHORISATION

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