Applicant: Teva Pharmaceuticals (Pty) Ltd	Product name: TACYL
Registration number: TACYL: 53/17.1/0630	Dosage form & strength: Each vial contains 50 mg tigecycline sterile powder for solution for intravenous infusion

PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

TACYL (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.

TACYL is sugar free.

For full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Sterile powder for solution for intravenous infusion.

TACYL is a lyophilised orange to orange-red cake or powder.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

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

The recommended duration of treatment with TACYL 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 TACYL 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 TACYL in patients with severe hepatic impairment (Child Pugh C), the dose of TACYL 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 children:

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**).

Use in elderly:

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**).

Method of administration:

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

For instructions on reconstitution & dilution of TACYL before administration, see **section 6.6**.

4.3 Contraindications:

- Hypersensitivity to tigecycline or to any of the excipients listed in **section 6.1**.
- Patients hypersensitive to tetracycline class antibiotics may be hypersensitive to tigecycline.
- 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. TACYL) 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 TACYL 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 TACYL due to the underlying conditions or concomitant medicines, a possible contribution of TACYL should be considered (see **section 4.8**).

Tetracycline class antibiotics:

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. TACYL 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, azotaemia, acidosis, and hyperphosphataemia (see **section 4.8**).

Pancreatitis:

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

Underlying diseases:

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

Consideration should be given to the use of combination antibacterial therapy whenever TACYL 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 TACYL 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 TACYL 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 shown bone discolouration. TACYL may be associated with permanent tooth discolouration in humans if used during tooth development (see **section 4.8**).

Paediatric population:

Clinical experience in the use of tigecycline for the treatment of infections in paediatric patients aged 8 years and older is very limited (see **sections 4.8** and **5.1**). Consequently, use in children should be restricted to those clinical situations where no alternative antibacterial therapy is available.

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

Abdominal pain is frequently 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 TACYL and regularly while on treatment.

TACYL should not be used in children due to the lack of safety and efficacy data in this age group and because tigecycline may be associated with permanent teeth discolouration (see **sections 4.2** and **4.8**).

4.5 Interaction with other medicines and other forms of interaction:

Concomitant administration of TACYL (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. TACYL did not significantly alter the effects of warfarin on increased international normalised ratio (INR). In addition, warfarin did not affect the pharmacokinetic profile of TACYL. However, prothrombin time or other suitable anticoagulation test should be monitored if TACYL is administered with warfarin.

TACYL 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 (see **section 5.2**).

TACYL (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. TACYL 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 TACYL. Therefore, no dosage adjustment is necessary when TACYL is 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 TACYL in pregnant women. Studies in animals have shown reproductive toxicity (see **section 5.3**).

TACYL 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 (see **section 5.3**).

TACYL 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	FREQUENT:	LESS FREQUENT:	FREQUENCY

CLASS:			UNKNOWN:
Infections and infestations	Sepsis/septic shock, pneumonia, abscess, infections		
Blood and lymphatic system disorders	Prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time (PT)	Thrombocyto-penia, 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		
Vascular disorders	Phlebitis	Thrombophlebitis	
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, anorexia	Acute pancreatitis (see **section 4.4**)	
Hepato-biliary disorders	Elevated aspartate	Jaundice, liver	Hepatic failure*

	aminotransferase (AST) in serum, and elevated alanine aminotransferase (ALT) in serum, hyperbilirubinaemia	injury, mostly cholestatic	(see **section 4.4**)
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**).

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

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.

The information below provides only approximate guidance on the probability as to whether the microorganism will be susceptible to tigecycline or not:

Susceptibility:

Gram-positive aerobes:

*Enterococcus faecalis** (includes vancomycin-susceptible strains)

*Staphylococcus aureus** (includes methicillin-susceptible and -resistant strains, including isolates that bear molecular and virulence markers commonly associated with community acquired MRSA including the SCCmec type IV element and the pvl gene)

*Streptococcus agalactiae**

*Streptococcus anginosus** (includes *S. anginosus*, *S. intermedius*, *S. constellatus*)

*Streptococcus pyogenes**

Gram-negative aerobes:

*Citrobacter freundii**

*Enterobacter cloacae**

*Escherichia coli**

*Klebsiella oxytoca**

*Klebsiella pneumoniae**

Anaerobic bacteria:

*Bacteroides fragilis**

*Bacteroides thetaiotaomicron**

*Bacteroides uniformis**

*Bacteroides vulgatus**

Clostridium perfringens

Peptostreptococcus micros

Species for which acquired resistance may be a problem:

Gram-negative Aerobes:

Acinetobacter baumannii

Burkholderia cepacia

Enterobacter aerogenes

*Enterobacter cloacae**

*Klebsiella pneumoniae**

Morganella morganii

Proteus spp.

Providencia spp.

Serratia marcescens

Stenotrophomonas maltophilia

Anaerobes:

Bacteroides fragilis group

Inherently resistant organisms:

Gram-negative Aerobes:

Pseudomonas aeruginosa

*Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.

5.2 Pharmacokinetic properties:

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.

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 14C-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* medicine 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 ciclosporin) or P-gp inducers (e.g., rifampicin) could affect the pharmacokinetics of tigecycline.

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 55 % and the half-life of tigecycline was prolonged by 23 % and 43 % 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**).

Paediatric population:

Population PK analysis of studies performed identified body weight as a covariate of tigecycline clearance in children aged 8 years and older. A dosing regimen of 1,2 mg/kg of tigecycline every 12 hours (to a maximum

dose of 50 mg every 12 hours) for children aged 8 to <12 years and of 50 mg every 12 hours for adolescents aged 12 to <18 years would likely result in exposures comparable to those observed in adults treated with the approved dosing regimen.

Higher C_{max} values than in adult patients were observed in several children in studies performed. As a consequence, care should be paid to the rate of infusion of tigecycline in children and adolescents.

Gender:

Studies performed indicate no clinically relevant differences in the clearance of tigecycline between men and women. AUC was estimated to be 20 % higher in females than in males.

Race:

There were no differences in the clearance of tigecycline 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.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

L-arginine

6.2 Incompatibilities:

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

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

6.3 Shelf life:

2 years.

Reconstituted solution:

Once reconstituted with 0,9 % Sodium chloride injection, Dextrose 5% or Ringer Lactate, TACYL powder for solution for infusion should be used immediately. If storage is necessary, TACYL power for solution for infusion mixed with 0,9 % Sodium chloride injection or Dextrose 5 % may be stored refrigerated at 2 ºC to 8 ºC for up to 48 hours following immediate transfer of the reconstituted solution into the intravenous bag.

6.4 Special precautions for storage:

Store at or below 25 °C.

Protect from light and moisture.

Keep the container tightly closed and keep in the carton until required for use.

Do not refrigerate or freeze.

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

6.5 Nature and contents of container:

TACYL 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.

TACYL is supplied in a cardboard unit carton as a pack size of 10 vials.

6.6 Special precautions for disposal and other handling:

The powder should be reconstituted with 5,3 ml of sodium chloride 9 mg/ml (0,9 %) solution for injection, dextrose 50 mg/ml (5 %) solution for injection, or Lactated Ringer's solution for injection to achieve a

concentration of 10 mg/ml of TACYL. The vial should be gently swirled until the medicine is dissolved. Thereafter, 5 ml of the reconstituted solution should be immediately withdrawn from the vial and added to a 100 ml intravenous bag for infusion or other suitable infusion container (e.g., glass bottle).

For a 100 mg dose, reconstitute using two vials into a 100 ml intravenous bag or other suitable infusion container (e.g., glass bottle). Note: The vial contains a 6 % overage. Thus, 5 ml of reconstituted solution is equivalent to 50 mg of the active substance. The reconstituted solution should be yellow to orange in colour; if not, the solution should be discarded. Parenteral products should be inspected visually for particulate matter and discolouration (e.g., green or black) prior to administration.

TACYL should be administered intravenously through a dedicated line or through a Y-site. If the same intravenous line is used for sequential infusion of several active substances, the line should be flushed before and after infusion of TACYL with either sodium chloride 9 mg/ml (0,9 %) solution for injection or dextrose 50 mg/ml (5 %) solution for injection. Injection should be made with an infusion solution compatible with TACYL and any other medicines via this common line (see **section 6.2**)

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

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.

When administered through a Y-site, compatibility of TACYL diluted in sodium chloride 0,9 % for injection is demonstrated with the following medicines or diluents: amikacin, dobutamine, dopamine HCl, gentamicin, haloperidol, Lactated Ringer's, lidocaine HCl, metoclopramide, morphine, norepinephrine, piperacillin/tazobactam (EDTA formulation), potassium chloride, propofol, ranitidine HCl, theophylline, and tobramycin.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park, Magwa Crescent West,

Waterfall City, Midrand,

South Africa,

2090

8. REGISTRATION NUMBER(S):

TACYL: 53/17.1/0630

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

13 September 2022

10. DATE OF REVISION OF THE TEXT: