SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

TYGACIL 50 mg Sterile powder for intravenous infusion

2. QUANTITATIVE AND QUALITATIVE COMPOSITION

Each 5 mL vial contains 50 mg tigecycline.

Contains sugar (lactose monohydrate).

Excipients with known effect

Each 5 mL vial contains 106 mg lactose monohydrate.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Sterile powder for intravenous infusion.

TYGACIL is an orange lyophilised powder or cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

The recommended duration of treatment with TYGACIL 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 TYGACIL is necessary in patients with renal impairment or in patients undergoing haemodialysis (see section 5.2, Pharmacokinetic properties, *Special populations, 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 TYGACIL in patients with severe hepatic impairment (Child Pugh C), the dose of TYGACIL 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, Pharmacokinetic properties, *Special populations, Hepatic insufficiency*).

Elderly population

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

Paediatric population

Clinical trials to establish the safety and effectiveness of TYGACIL 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

TYGACIL is contraindicated for use

- in patients who have known hypersensitivity to tigecycline or to any of the excipients of TYGACIL (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 Phase 3 and 4 clinical trials in TYGACIL treated patients versus comparator-treated patients. In a pooled analysis of 13 Phase 3 and 4 trials that included a comparator, death occurred in 4,0 % (150/3788) of patients receiving TYGACIL and 3,0 % (110/3646) of patients receiving comparator medicines resulting in an unadjusted risk difference of 0,9 % (95 % CI 0,1; 1,8). 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 % (95 % CI 0,1; 1,2) between TYGACIL 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.

TYGACIL should not be used in hospital associated pneumonia (HAP) or ventilator associated pneumonia (VAP). The safety and efficacy of TYGACIL 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 TYGACIL (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 TYGACIL had lower cure rates (47,9 % versus 70,1 % for the clinically evaluable population) and higher mortality (25/131 [19,1 %] versus 15/122 [12,3 %]) than the comparator. Of those patients with ventilator-associated pneumonia and bacteraemia at baseline, those who received TYGACIL had greater mortality (9/18 [50,0 %] versus 1/13 [7,7 %]) than the comparator. Of those patients with ventilator-associated pneumonia and bacteraemia at baseline, those who received TYGACIL had greater mortality (9/18 [50,0 %] versus 1/13 [7,7 %]) than the comparator.

Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial medicines, including TYGACIL, and may be life-threatening**.**

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

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

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

Caution should be exercised when considering TYGACIL monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In Phase 3

and 4 cIAI studies (n=2775), 140/1382 TYGACIL -treated patients and 142/1393 comparator-treated patients presented with intestinal perforations. Of these patients, 8/140 patients treated with TYGACIL and 8/142 patients treated with comparator developed sepsis/septic shock. The relationship of this outcome to treatment cannot be established.

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

Glycylcycline class antibiotics 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). Pancreatitis has been reported with the use of TYGACIL.

Acute pancreatitis, which can be fatal, has occurred in association with TYGACIL treatment. The diagnosis of acute pancreatitis should be considered in patients taking TYGACIL 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 TYGACIL discontinuation. Cessation of the treatment with TYGACIL in cases suspected of having developed pancreatitis is advised.

Coagulopathy

TYGACIL may prolong both prothrombin time (PT) and activated partial thromboplastin time (aPTT). Additionally, hypofibrinogenaemia has been reported with the use of TYGACIL. Therefore, blood coagulation parameters such as PT or other suitable anticoagulation test, including blood fibrinogen, should be monitored prior to treatment initiation with TYGACIL and regularly while on treatment. Special care is recommended in seriously ill patients and in patients also using anticoagulants (see section 4.5).

Use of TYGACIL 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.

Paediatric use

Clinical trials to establish the safety and effectiveness of TYGACIL 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 the elderly

In a pooled analysis of 3 900 subjects who received TYGACIL in Phase 3 and 4 clinical studies, 1 026 were 65 years and over. Of these 419 were 75 years and over. 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 5 mL of suspension, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

TYGACIL (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. TYGACIL 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 TYGACIL. Therefore, no dosage adjustment is necessary when TYGACIL is administered with digoxin.

Concomitant administration of TYGACIL (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. TYGACIL did

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

In vitro studies in human liver microsomes indicate that TYGACIL does not inhibit metabolism mediated by any of the following 6 cytochrome CYP450 isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. Therefore, TYGACIL is not expected to alter the metabolism of medicines metabolised by these enzymes. In addition, because TYGACIL is not extensively metabolised, clearance of TYGACIL 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 TYGACIL does not inhibit digoxin flux, suggesting that TYGACIL is not a P-glycoprotein (P-gp) inhibitor. This *in vitro* information is consistent with the lack of effect of TYGACIL on digoxin clearance noted in the *in vivo* drug interaction study described above.

TYGACIL 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 TYGACIL is not known. Coadministration of P-gp inhibitors (e.g., ketoconazole or ciclosporin) or P-gp inducers (e.g., rifampicin) could affect the pharmacokinetics of TYGACIL.

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

Concomitant use of TYGACIL 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 TYGACIL 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

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

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

Breastfeeding

Results from animal studies using ^{14}C-labeled TYGACIL indicate that TYGACIL is excreted readily via the milk of lactating rats. It is not known whether this medicine is excreted in human milk. Therefore, TYGACIL 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).

4.8 Undesirable effects

Tabulated summary of adverse reactions

Expected frequency of adverse reactions is presented in CIOMS frequency categories: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

For patients who received TYGACIL, the following adverse reactions were reported:

System organ class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	Common	Prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time (PT), thrombocytopenia

	Uncommon	Increased international normalised ratio (INR)
	Rare	Hypofibrinogenaemia
Immune system disorders	Frequency undetermined	Anaphylaxis / anaphylactoid reactions
Metabolism and nutrition disorders	Common	Hypoproteinaemia, hypoglycaemia
Nervous system disorders	Common	Dizziness
Vascular disorders	Common	Phlebitis
	Uncommon	Thrombophlebitis
Respiratory, thoracic and mediastinal disorders	Common	Pneumonia
Gastrointestinal disorders	Very common	Nausea, vomiting, diarrhoea
	Common	Anorexia, abdominal pain, dyspepsia
	Uncommon	Acute pancreatitis
Hepato-biliary disorders	Common	Elevated aspartate aminotransferase (AST) in serum, elevated alanine aminotransferase (ALT) in serum*, hyperbilirubinaemia
	Uncommon	Jaundice
	Frequency Undetermined	Hepatic cholestasis
Skin and subcutaneous tissue disorders	Common	Pruritus, rash
	Frequency undetermined	Severe skin reactions, including Stevens-Johnson Syndrome
General disorders and administration site	Common	Headache, impaired healing, injection site reaction

conditions	Uncommon	Injection site inflammation, injection site pain, injection site oedema, injection site phlebitis
Investigations	Common	Elevated amylase in serum, increased blood urea nitrogen (BUN)
* AST and ALT abnormalities in TYGACIL treated patients were reported more frequently in the post therapy period than in those in comparator-treated patients, which occurred more often on therapy.		

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), or fixed eruption.

In a pooled analysis of all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4,0 % (150/3788) of patients receiving TYGACIL and 3,0 % (110/3646) of subjects receiving comparator medicines. In a pooled analysis of these trials, the risk difference of all-cause mortality was 0,9 % (95 % CI 0,1; 1,8) between TYGACIL and comparator-treated subjects. 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 % (95 % CI 0,1; 1,2) between TYGACIL -treated and comparator-treated subjects. No significant differences were observed between TYGACIL and comparators within each infection

type. The cause of the imbalance has not been established. Generally, deaths were the result of worsening infection, or complications of infection or underlying co-morbidities.

The most common treatment-emergent adverse reactions, in patients treated with TYGACIL were nausea 29,9 % [19,3 % mild; 9,2 % moderate; 1,4 % severe] and vomiting 19,9 % [12,1 % mild; 6,8 % moderate; 1,1 % severe]. In general, nausea or vomiting occurred early (days 1 – 2).

Discontinuation from TYGACIL was most frequently associated with nausea (1,6 %) and vomiting (1,3 %).

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.

Report any suspected adverse drug reactions associated with the use of the medicine directly to Pfizer via ZAF.AEReporting@pfizer.com.

4.9 Overdose

No specific information is available on the treatment of overdose with TYGACIL. Intravenous administration of TYGACIL at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. TYGACIL 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, 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.

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

	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

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 ^{14}C-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.

Two studies examined the steady-state pharmacokinetic profile of tigecycline in specific tissues or fluids of healthy subjects receiving tigecycline 100 mg loading dose followed by six 50 mg doses every 12 hours. In a bronchoalveolar lavage study, samples were collected by standardised bronchoscopy at 2, 3, 4, 6, 12 and 24 hours after administration of the last dose. The tigecycline $AUC_{0\text{-}12h}$ (134 μg·h/mL) in alveolar cells was approximately 77,5-fold higher than the $AUC_{0\text{-}12h}$ in the serum of these subjects, and the $AUC_{0\text{-}12h}$ (2,28 μg·h/mL) in epithelial lining fluid was approximately 32 % higher than the $AUC_{0\text{-}12h}$ in serum. In a skin blister study, blood and blister samples were collected at 0,5, 1, 2, 3, 4, 6, 8, 12 and 24 hours after the last dose. The $AUC_{0\text{-}12h}$ (1,61 μg·hr/mL) of tigecycline in skin blister fluid was approximately 26 % lower than the $AUC_{0\text{-}12h}$ in the serum of these subjects.

In a single-dose study, tigecycline 100 mg was administered to subjects prior to undergoing elective surgery or medical procedure for tissue extraction. Tissue concentrations at 4 hours after tigecycline administration were measured in the following tissue and fluid samples: gallbladder, lung, colon, synovial fluid, and bone. Tigecycline attained higher concentrations in tissues versus serum in gallbladder (38-fold, n=6), lung (3,7-fold, n=5), and colon (2,3-fold, n=6). The concentration of tigecycline in these tissues after multiple doses has not been studied.

Metabolism

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.

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.

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.

Special populations

Hepatic insufficiency

In a study comparing 10 patients with mild hepatic impairment (Child Pugh A), 10 patients with moderate hepatic impairment (Child Pugh B), and 5 patients with severe hepatic impairment (Child Pugh C) to 23 age- and weight-matched healthy control subjects, the single-dose pharmacokinetic disposition of tigecycline was not altered in patients with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25 %, and the half-life of tigecycline was prolonged by 23 % in patients with moderate hepatic impairment (Child Pugh B). 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, *Use in patients with hepatic impairment*).

Renal insufficiency

A single-dose study compared 6 subjects with severe renal impairment (creatinine clearance CrCl ≤ 30 mL/min), 4 end stage renal disease patients receiving tigecycline 2 hours before haemodialysis, 4 end stage renal disease patients receiving tigecycline after haemodialysis, and 6 healthy control subjects. The pharmacokinetic profile of tigecycline was not altered in any of the renally impaired

patient groups, nor was tigecycline removed by haemodialysis. No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing haemodialysis (see section 4.2, *Use in patients with renal impairment*).

Elderly

No overall differences in pharmacokinetics were 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, *Use in the elderly*).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Sodium hydroxide for pH adjustment

Hydrochloric acid for pH adjustment

6.2 Incompatibilities

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

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

Once reconstituted in the IV bag, TYGACIL may be stored at room temperature (not to exceed 25 °C) for up to 24 hours (up to 6 hours in the vial and the remaining time in the IV bag). Alternatively, TYGACIL mixed with 0,9 % Sodium Chloride Injection USP or 5 % Dextrose Injection USP, may be stored refrigerated at 2 °C to 8 °C for up to 48 hours following immediate transfer of the reconstituted

solution into the IV bag.

If the storage conditions exceed 25 °C after reconstitution, TYGACIL should be used immediately. Reconstituted solution must be transferred and further diluted for IV infusion.

6.5 Nature and contents of the pack

TYGACIL is packaged in Type I clear glass vials fitted with grey butyl rubber stoppers and snap-off aluminium crimp seals.

TYGACIL is supplied in a cardboard unit carton containing 10 vials. Each single-dose, 5 mL glass vial contains 50 mg lyophilised powder for infusion.

6.6 Special precautions for disposal and handling

Compatible intravenous solutions include 0,9 % Sodium Chloride Injection USP, 5 % Dextrose Injection USP and Lactated Ringer's Injection USP.

TYGACIL 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, metoclopramide, morphine, noradrenaline, piperacillin/tazobactam (EDTA formulation) potassium chloride, propofol, ranitidine HCl, theophylline and tobramycin.

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 Injection USP to achieve a concentration of 10 mg/mL of TYGACIL. 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 medicine products should be inspected visually for particulate matter and discolouration (e.g., green or black) prior to administration whenever solution and container permit. Once reconstituted TYGACIL may be stored at room temperature (not to exceed 25 ºC) for up to 24 hours (up to 6 hours in the vial and the remaining time in the IV bag). Alternatively, TYGACIL mixed with 0,9 % Sodium Chloride Injection USP or 5 % Dextrose Injection USP, may be stored refrigerated at 2 ºC – 8 ºC for up to 48 hours following immediate transfer of the reconstituted solution into the IV bag.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBER

A40/20.1.1/0230

9. DATE OF FIRST AUTHORISATION

08 June 2007

10. DATE OF REVISION OF THE TEXT

02 October 2026

NAMIBIA: S2

Reg. No.: 08/20.1.1/0175

BOTSWANA: S2

Reg. No.: BOT0901578

Manufacturer:

Patheon Italia S.p.A.

Wyeth Lederle S.r.l.