SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form)

TYGACIL® 50 mg Sterile Powder for Intravenous Infusion

COMPOSITION

Each 5 ml vial contains 50 mg tigecycline.

PHARMACOLOGICAL CLASSIFICATION

A 20.1.1 Broad and Medium Spectrum Antibiotics

PHARMACOLOGICAL ACTION

Mode 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.

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

Susceptible

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**

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

Pharmacokinetics

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	Multiple Dose[c]
	100 mg	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 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 followed by 50 mg every 12 hours. In a bronchoalveolar lavage study, 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, 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

(8,6-fold, n=1), and colon (2,1-fold, n=5). The concentration of tigecycline in these tissues after multiple doses has not been studied.

Metabolism

Tigecycline is not extensively metabolized. *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.

<u>Special Populations</u>

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 five 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 tigecycyline 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 DOSAGE AND DIRECTIONS FOR USE, Use in patients with hepatic impairment.)

Renal insufficiency

A single-dose study compared six subjects with severe renal impairment (creatinine clearance Cl_{Cr} ≤ 30 ml/min), four end stage renal disease patients receiving tigecycline 2 hours before haemodialysis, four end stage renal disease patients receiving tigecycline after haemodialysis, and six 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 DOSAGE AND DIRECTIONS FOR USE, Use in patients with renal impairment.)

Elderly

No overall differences in pharmacokinetics were observed between healthy elderly subjects (n=15, age 65 - 75; n=13, age > 75, and younger subjects (n=18) receiving a single, 100 mg dose of tigecycline. Therefore, no dosage adjustment is necessary based on age.

Children

The pharmacokinetics of tigecycline in patients less than 18 years of age have not been established.

Gender

In a pooled analysis of 38 women and 298 men participating in clinical pharmacology studies, there was no significant difference in the mean (±SD) tigecycline clearance between women (20,7±6,5 L/h) and men (22,8±8,7 L/h). Therefore, no dosage adjustment is necessary based on gender.

Race

In a pooled analysis of 73 Asian subjects, 53 Black subjects, 15 Hispanic subjects, 190 White subjects, and 3 subjects classified as “other” participating in clinical pharmacology studies, there was no significant difference in the mean (±SD) tigecycline clearance among the Asian subjects (28,8±8,8 L/h), Black subjects (23,0±7,8 L/h), Hispanic subjects (24,3±6,5 L/h), White subjects (22,1±8,9 L/h), and “other” subjects (25,0±4,8 L/h). Therefore, no dosage adjustment is necessary based on race.

INDICATIONS

TYGACIL 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*.

CONTRA-INDICATIONS

TYGACIL is contra-indicated for use in patients who have known hypersensitivity to **TYGACIL.**

Pregnancy and Lactation.

WARNINGS

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

Glycylcycline class antibiotics are 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 the teeth 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**.

Effects on Activities Requiring Concentration and Performance

TYGACIL can cause dizziness (see SIDE EFFECTS AND SPECIAL PRECAUTIONS), which may impair the ability to drive and/or operate machinery.

Abuse and Dependence

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

INTERACTIONS

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 normalized 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 drugs metabolized by these enzymes. In addition, because **TYGACIL** is not extensively metabolized, clearance of **TYGACIL** is not expected to be affected by drugs that inhibit or induce the activity of these CYP450 isoforms.

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

Interference with Laboratory and Other Diagnostic Tests

There are no reported drug-laboratory test interactions.

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.

TYGACIL has not been studied for use during labour and delivery. (See CONTRA-INDICATIONS)

Lactation

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 drug is excreted in human milk. (See CONTRA-INDICATIONS)

DOSAGE AND DIRECTIONS FOR USE

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.

Use in patients with renal impairment

No dosage adjustment of **TYGACIL** is necessary in patients with renal impairment or in patients undergoing haemodialysis. (See PHARMACOKINETICS, 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 PHARMACOKINETICS, 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 WARNINGS.)

Use in elderly

No dosage adjustment is necessary in elderly patients. (See SIDE EFFECTS AND SPECIAL PRECAUTIONS, Geriatric Use.)

Race and gender

No dosage adjustment is necessary based on race or gender. (See PHARMACOKINETICS.)

Mode of administration

Intravenous infusion.

Compatibilities, Incompatibilities, 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 drugs 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.

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

The lyophilized 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 **TYGACIL**. The vial should be gently swirled until the drug 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 drug). The reconstituted solution should be yellow to orange in colour; if not, the solution should be discarded. Parenteral drug 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 for up to 24 hours (up to 6 hours in the vial and the remaining time in the I.V. bag). Alternatively **TYGACIL** mixed with 0,9 % Sodium Chloride Injection, USP or 5 % Dextrose Injection, USP, may be stored refrigerated at 2 ^{0}C – 8 ^{0}C for up to 48 hours following immediate transfer of the reconstituted solution into the I.V. 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 drugs, 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 drug(s) administered via this common line.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

Expected frequency of adverse reactions is presented in CIOMS frequency categories:

Very Common	≥ 10 %
Common:	≥ 1 % and < 10 %
Uncommon:	≥ 0,1 % and < 1 %
Rare:	≥ 0,01 % and < 0,1 %
Very rare:	< 0,01 %

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

System Organ Class	***Adverse Reaction***
Blood and lymphatic system disorders	
Common	Prolonged activated partial thromboplastin time (aPTT), Prolonged prothrombin time (PT)
Uncommon	Increased international normalized ratio (INR)

System Organ Class	*Adverse Reaction*
Immune system disorders	
Frequency undetermined	Anaphylaxis/anaphylactoid reactions
Metabolism and nutrition disorders	
Common	Bilirubinaemia, increased Blood Urea Nitrogen (BUN)
Uncommon	Hypoproteinaemia
Nervous system disorders	
Common	Dizziness
Cardiac disorders	
Common	Phlebitis
Uncommon	Thrombophlebitis
Gastrointestinal disorders	
Very common	Nausea, vomiting, diarrhoea
Common	Anorexia, abdominal pain, dyspepsia
Uncommon	Acute pancreatitis
Hepato-biliary disorders	

System Organ Class	***Adverse Reaction***
Common	Elevated aspartate aminotransferase (AST) in serum, elevated alanine aminotransferase (ALT) in serum*
Frequency undetermined	Hepatic cholestasis

* 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.

Skin and subcutaneous tissue disorders

Common	Pruritus, rash

General disorders and administration site conditions

Common	Headache
Uncommon	Injection site inflammation, injection site pain, injection site reaction, injection site oedema, injection site phlebitis

Investigations

Common	Elevated amylase in serum

In Phase 3 double blind studies that included a comparator and employed a 1:1 randomisation, death occurred in 4,7 % (107/2274) of patients receiving **TYGACIL** and 3,8 % (85/2264) of patients receiving comparator drugs. In a pooled analysis of these studies, the risk difference of all cause mortality was 1,0 % (95 % CI – 0,3; 2,2) between **TYGACIL** and comparator treated patients. No significant differences were observed between treatments by infection type (see Table 2). Generally, deaths represented complications of the underlying disease or progression of disease. A causal relationship to **TYGACIL** has not been established.

Table 2: Patients with Adverse events with outcome of death by Infection type

	TYGACIL		Comparator		Risk Difference*
Infection type	n/N	%	n/N	%	% (95 % CI)
cSSSI	6/566	1,1	1/550	0,2	0,9 (-0,3; 2,2)
cIAI	24/817	2,9	17/825	2,1	0,9 (-0,8; 2,6)
CAP	12/424	2,8	11/422	2,6	0,2 (-2,3; 2,7)
HAP	65/467	13,9	56/467	12,0	1,9 (-2,6; 6,4)
Non-VAP[a]	40/336	11,9	42/345	12,2	-0,3 (-5,4; 4,9)
VAP[a]	25/131	19,1	14/122	11,5	7,6 (-2,0; 16,9)

CAP= Community-acquired pneumonia; cIAI= Complicated intra-abdominal infections; cSSSI= Complicated skin and skin structure infections; HAP = hospital-acquired pneumonia; VAP = ventilator-associated pneumonia.
* The difference between the percentage of patients who died in **TYGACIL** and comparator treatment groups
a These are the subgroups of the HAP population
Note: The Phase 3 Studies include 300 and 305 (cSSSI), 301 and 306 (cIAI), 308 and 313 (CAP), 311 (HAP)

The most common drug-related treatment emergent adverse events, in patients treated with **TYGACIL** were nausea 20,4 % (12,9 % mild; 6,6 % moderate; 0,8 % severe) and vomiting 13,5 % (8,3 % mild; 4,5 % moderate; 0,6 % severe). In general, nausea or vomiting occurred early (days 1 - 2).

Discontinuation from **TYGACIL** was most frequently associated with nausea (1, 3 %) and vomiting (1,0 %).

SPECIAL PRECAUTIONS

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 cIAI studies (n=1642), six patients treated with **TYGACIL** and two patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The six patients treated with **TYGACIL** had higher APACHE II scores (median =13) vs the two patients treated with imipenem/cilastatin (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, 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 are 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, azotaemia, acidosis, and hyperphosphataemia). As with tetracycline, pancreatitis has been reported with the use of **TYGACIL**.

The safety and efficacy of **TYGACIL** in patients with hospital acquired pneumonia have not been established. In a study of patients with hospital acquired pneumonia, patients were randomized 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 who received **TYGACIL**

had lower cure rates (47,9 % versus 70,1 % for the clinically evaluable population) and greater mortality (25/131 [19,1 %] versus 14/122 [11,5 %] than the comparator.

Use of **TYGACIL** 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.

Paediatric Use

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 SPECIAL WARNINGS.)

Geriatric Use

Of the total number of subjects who received **TYGACIL** in Phase 3 clinical studies (n=1415), 278 were 65 and over, while 110 were 75 and over. No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

No specific information is available on the treatment of overdosage 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.

IDENTIFICATION

TYGACIL is an orange lyophilized powder or cake.

PRESENTATION

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.

STORAGE INSTRUCTIONS

TYGACIL should be stored at 20 °C to 25 °C prior to reconstitution. Once reconstituted in the I.V. bag, **TYGACIL** 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, **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.

Reconstituted solution must be transferred and further diluted for I.V. infusion.

REGISTRATION NUMBER

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NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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