Product Information as approved by the CHMP on 17 February 2011, pending endorsement by the European Commission

Deleted text highlighted in ~~**red strikethrough**~~, added text highlighted in **red bold**.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tygacil 50 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml Tygacil vial contains 50 mg of tigecycline. After reconstitution, 1 ml contains 10 mg of tigecycline.

~~Excipient(s) :~~
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion **(powder for infusion)**.

Lyophilised orange cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tygacil is indicated **in adults** for the treatment of the following infections (see sections 4.4 and 5.1):

- Complicated skin and soft tissue infections, excluding diabetic foot infections (see section 4.4)
- Complicated intra-abdominal infections

Tygacil should be used only in situations where it is known or suspected that other alternatives are not suitable (see sections 4.4 and 4.8).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The recommended dose for adults is an initial dose of 100 mg followed by 50 mg every 12 hours for 5 to 14 days.

The duration of therapy should be guided by the severity, site of the infection, and the patient's clinical response.

Hepatic insufficiency
No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B).

In patients with severe hepatic impairment (Child Pugh C), the dose of Tygacil should be reduced to 25 mg every 12 hours following the 100 mg loading dose. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response (see sections 4.4 and 5.2).

Renal insufficiency
No dosage adjustment is necessary in patients with renal impairment or in patients undergoing haemodialysis (see section 5.2).

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

Paediatric ~~patients~~ ***population***
~~Tygacil is not recommended for use in children and adolescents below 18 years due to the lack of data on safety and efficacy~~ **The safety and efficacy of Tygacil in children below 18 years have not yet been established. No data are available** (see sections 5.2 and 4.4).

Method of administration:

Tygacil is administered only by intravenous infusion over 30 to 60 minutes (see section 6.6).

For instructions on reconstitution & dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Patients hypersensitive to tetracycline class antibiotics may be hypersensitive to tigecycline.

4.4 Special warnings and precautions for use

In clinical studies in complicated skin and soft tissue infections, complicated intra-abdominal infections, diabetic foot infections, nosocomial pneumonia and studies in resistant pathogens, a numerically higher mortality rate among Tygacil 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.

Patients who develop super-infections, in particular nosocomial pneumonia, appear to be associated with poorer outcomes. Patients should be closely monitored for the development of super-infection. If a focus of infection other than cSSTI or cIAI is identified after initiation of Tygacil 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.

Tygacil is not approved for clinical indications other than complicated skin and soft tissue infections, and complicated intra-abdominal infections. The use of Tygacil in non-approved indications is not recommended.

Anaphylaxis/anaphylactoid reactions, potentially life-threatening, have been reported with tigecycline (see sections 4.3 and 4.8).

Cases of liver injury with a predominantly cholestatic pattern have been reported in patients receiving tigecycline treatment, including some cases of hepatic failure with a fatal outcome. Although hepatic failure may occur in patients treated with tigecycline due to the underlying conditions or concomitant ~~medications~~ **medicinal products**, a possible contribution of tigecycline should be considered (see section 4.8).

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. Tigecycline 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).

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 tigecycline who develop clinical symptoms, signs, or laboratory abnormalities suggestive of acute pancreatitis. Most of the reported cases developed after at least one week of treatment. Cases have been reported in patients without known risk factors for pancreatitis. Patients usually improve after tigecycline discontinuation. Consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis.

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

In clinical trials in complicated skin and soft tissue infections, the most common type of infection in tigecycline treated-patients was cellulitis (59 %), followed by major abscesses (27.5 %). Patients with severe underlying disease, such as those that were immunocompromised, patients with decubitus ulcer infections, or patients that had infections requiring longer than 14 days of treatment (for example, necrotizing fasciitis), were not enrolled. A limited number of patients were enrolled with co-morbid factors such as diabetes (20 %), peripheral vascular disease (7 %), intravenous drug abuse (2 %), and HIV-positive infection (1 %). Limited experience is also available in treating patients with concurrent bacteraemia (3 %). Therefore, caution is advised when treating such patients. The results in a large study in patients with diabetic foot infection, showed that tigecycline was less effective than comparator, therefore, tigecycline is not recommended for use in these patients (see section 4.1).

In clinical trials in complicated intra-abdominal infections, the most common type of infection in tigecycline treated-patients was complicated appendicitis (51 %), followed by other diagnoses less commonly reported such as complicated cholecystitis (14 %), intra-abdominal abscess (10 %), perforation of intestine (10 %) and gastric or duodenal ulcer perforation less than 24 hours (5 %). Of these patients, 76 % had associated diffuse peritonitis (surgically-apparent peritonitis). There were a limited number of patients with severe underlying disease such as immunocompromised patients, patients with APACHE II scores > 15 (4 %), or with surgically apparent multiple intra-abdominal abscesses (10 %). Limited experience is also available in treating patients with concurrent bacteraemia (6 %). Therefore, caution is advised when treating such patients.

Consideration should be given to the use of combination antibacterial therapy whenever tigecycline is to be administered to severely ill patients with complicated intra-abdominal 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 has not been properly established. Biliary excretion accounts for approximately 50 % of the total tigecycline excretion. Therefore, patients presenting with cholestasis should be closely monitored.

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

Pseudomembranous colitis has been reported with nearly all antibacterial agents 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 agent (see section 4.8).

The use of tigecycline 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. Tigecycline may be associated with permanent tooth discolouration in humans if used during tooth development (see section 4.8).

Paediatric population

Tygacil should not be used in children under 8 years of age because of teeth discolouration, and is not recommended in adolescents below 18 years due to the lack of data on safety and efficacy (see sections 4.2 and 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Concomitant administration of tigecycline 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. The mechanism of this interaction is still not elucidated. Available data does not suggest that this interaction may result in significant INR changes. However, since tigecycline may prolong both prothrombin time (PT) and activated partial thromboplastin time (aPTT), the relevant coagulation tests should be closely monitored when tigecycline is co-administered with anticoagulants (see section 4.4). Warfarin did not affect the pharmacokinetic profile of tigecycline.

Tigecycline 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).

Tigecycline in recommended dosage did not affect the rate or extent of absorption, or clearance of digoxin (0.5 mg followed by 0.25 mg daily) when administered in healthy adults. Digoxin did not affect the pharmacokinetic profile of tigecycline. Therefore, no dosage adjustment is necessary when tigecycline 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of tigecycline in pregnant women. Results from animal studies have shown tigecycline may cause foetal harm when administered during pregnancy (see section 5.3). The potential risk for humans is unknown. As it is known for tetracycline class antibiotics, tigecycline may also induce permanent dental defects (discolouration and enamel defects) and a delay in ossification processes in foetuses, exposed *in utero* during the last half of gestation, and in children under eight years of age due to the enrichment in tissues with a high calcium turnover and formation of calcium chelate complexes (see section 4.4). Tigecycline should not be used during pregnancy unless clearly necessary.

Breastfeeding

It is not known whether this medicinal product is excreted in human milk. In animal studies tigecycline is excreted into milk of lactating rats. Because a potential risk to the breast-feeding infant cannot be ruled out, when treating with tigecycline, caution should be exercised and interruption of breast-feeding should be considered (see section 5.3).

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

No studies on the effects of tigecycline on the ability to drive and use machines have been performed. Dizziness may occur and this may have an effect on driving and use of machines (see section 4.8).

4.8 Undesirable effects

a. Summary of safety profile

The total number of patients treated with tigecycline in Phase 3 clinical studies was 1,415. Adverse reactions were reported in approximately 41 % of patients treated with tigecycline. Treatment was discontinued due to adverse reactions in 5 % of patients.

In clinical trials, the most common drug-related treatment emergent adverse reactions were reversible nausea (20 %) and vomiting (14 %), which usually occurred early (on treatment days 1-2) and were generally mild or moderate in severity.
Adverse reactions reported with Tygacil, including clinical trials and post-marketing experience, are listed below.

Frequency categories are expressed as: 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)**; Not known (cannot be estimated from the available data)**

For adverse reactions identified from post-marketing experience with Tygacil derived from spontaneous reports for which the frequency cannot be estimated, the frequency grouping is categorized as not known.

b. Tabulated summary of adverse reactions

Infections and infestations:

Common: Abscess, infections
Uncommon: Sepsis/septic shock
~~In Phase 3 clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with tigecycline (6.7 %) vs comparators (4.6 %). Significant differences in sepsis/septic shock with tigecycline (1.5 %) vs comparators (0.5 %) were observed.~~

Blood and the lymphatic system disorders:

Common: Prolonged activated partial thromboplastin time (aPTT), Prolonged prothrombin time (PT)
Uncommon: Increased International Normalised Ratio (INR)
Not known: thrombocytopenia

Immune system disorders:

Not known: Anaphylaxis/anaphylactoid reactions (see sections 4.3 and 4.4)

Metabolism and nutrition disorders:

Uncommon: Hypoproteinaemia

Nervous system disorders:

Common: Dizziness

Vascular disorders:

Common: Phlebitis

Uncommon: Thrombophlebitis

Gastrointestinal disorders:

Very common: Nausea, vomiting, diarrhoea
Common: Abdominal pain, dyspepsia, anorexia
Uncommon: Acute pancreatitis (see section 4.4)

Hepato-biliary disorders:

Common: Elevated aspartate aminotransferase (AST) in serum, and elevated alanine aminotransferase (ALT) in serum, hyperbilirubinaemia.
~~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.~~

Uncommon: Jaundice, liver injury, mostly cholestatic
Not known: Hepatic failure (see section 4.4)

Skin and subcutaneous tissue disorders:

Common: Pruritus, rash

General disorders and administration site conditions:

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

Investigations:

Common: Elevated amylase in serum, increased blood urea nitrogen (BUN)
~~In all Phase 3 and 4 cSSSI and cIAI studies, death occurred in 2.3 % (52/2216) of patients receiving tigecycline and 1.5% (33/2206) of patients receiving comparator drugs.~~

c. Description of selected adverse reactions

Antibiotic Class Effects:

Pseudomembranous colitis which may range in severity from mild to life threatening (see section 4.4)

Overgrowth of non-susceptible organisms, including fungi (see section 4.4)

Tetracycline Class Effects:

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. Tetracycline class adverse reactions may include photosensitivity, pseudotumour cerebri, pancreatitis, and anti-anabolic action which has led to increased BUN, azotaemia, acidosis, and hyperphosphataemia (see section 4.4).

Tigecycline may be associated with permanent tooth discolouration if used during tooth development (see section 4.4).

In Phase 3 clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with tigecycline (6.7 %) vs comparators (4.6 %). Significant differences in sepsis/septic shock with tigecycline (1.5 %) vs comparators (0.5 %) were observed.

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.

In all Phase 3 and 4 cSSSI and cIAI studies, death occurred in 2.3 % (52/2216) of patients receiving tigecycline and 1.5% (33/2206) of patients receiving comparator drugs.

4.9 Overdose

No specific information is available on the treatment of overdosage. Intravenous administration of tigecycline at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. Tigecycline is not removed in significant quantities by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: **Antibacterials for systemic use,**Tetracyclines~~, Antibacterials for systemic use~~ ATC code: J01AA12.

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.

In general, tigecycline is considered bacteriostatic. At 4 times the minimum inhibitory concentration (MIC), a 2-log reduction in colony counts was observed with tigecycline against *Enterococcus* spp., *Staphylococcus aureus*, and *Escherichia coli*.

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 multidrug 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.

Breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Staphylococcus spp. S ≤ 0.5 mg/L and R > 0.5 mg/L

Streptococcus spp. other than *S. pneumoniae* S ≤ 0.25 mg/L and R > 0.5 mg/L
Enterococcus spp. S ≤ 0.25 mg/L and R > 0.5 mg/L
Enterobacteriaceae S ≤ 1[(^)] mg/L and R > 2 mg/L

[(^)]Tigecycline has decreased *in vitro* activity against *Proteus, Providencia*, and *Morganella* spp.

For anaerobic bacteria there is clinical evidence of efficacy in polymicrobial intra-abdominal infections, but no correlation between MIC values, PK/PD data and clinical outcome. Therefore, no breakpoint for susceptibility is given. It should be noted that the MIC distributions for organisms of the genera Bacteroides and Clostridium are wide and may include values in excess of 2 mg/L tigecycline.

There is limited evidence of the clinical efficacy of tigecycline against enterococci. However, polymicrobial intra-abdominal infections have shown to respond to treatment with tigecycline in clinical trials.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Pathogen
Commonly Susceptible Species
Gram-positive Aerobes *Enterococcus* spp.† *Staphylococcus aureus** *Staphylococcus epidermidis* *Staphylococcus haemolyticus* *Streptococcus agalactiae** *Streptococcus anginosus* group* (includes *S. anginosus, S. intermedius and S. constellatus*) *Streptococcus pyogenes** Viridans group streptococci Gram-negative Aerobes *Citrobacter freundii** *Citrobacter koseri* *Escherichia coli** *Klebsiella oxytoca** Anaerobes *Clostridium perfringens*† *Peptostreptococcus* spp.† *Prevotella* spp.
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.

Pathogen
Serratia marcescens *Stenotrophomonas maltophilia* Anaerobes *Bacteroides fragilis* group†
Inherently resistant organisms
Gram-negative Aerobes *Pseudomonas aeruginosa*

*denotes species against which it is considered that activity has been satisfactorily demonstrated in clinical studies.
† see section 5.1, *Breakpoints* above.

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 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 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 2349±850 ng•h/ml.

~~Metabolism~~ **Biotransformation**

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

In vitro studies in human liver microsomes indicate that tigecycline does not inhibit metabolism mediated by any of the following 6 cytochrome P450 (CYP) isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4 by competitive inhibition. In addition, tigecycline did not show NADPH-dependency in the inhibition of CYP2C9, CYP2C19, CYP2D6 and CYP3A, suggesting the absence of mechanism-based inhibition of these CYP enzymes.

Elimination

The recovery of the total radioactivity in faeces and urine following administration of ^{14}C-tigecycline indicates that 59 % of the dose is eliminated by biliary/faecal excretion, and 33 % is excreted in urine. Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline. Glucuronidation and renal excretion of unchanged tigecycline are secondary routes.

The total clearance of tigecycline is 24 L/h after intravenous infusion. Renal clearance is approximately 13 % of total clearance. Tigecycline shows a polyexponential elimination from serum with a mean terminal elimination half-life after multiple doses of 42 hours although high interindividual variability exists.

Special populations

Hepatic Insufficiency
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).

Renal Insufficiency
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).

Elderly Patients
No overall differences in pharmacokinetics were observed between healthy elderly subjects and younger subjects (see section 4.2).

Paediatric ~~patients~~ ***population***
The pharmacokinetics of tigecycline in patients less than 18 years of age has not been established (see section 4.2).

Gender
There were 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.

5.3 Preclinical safety data

In repeated dose toxicity studies in rats and dogs, lymphoid depletion/atrophy of lymph nodes, spleen and thymus, decreased erythrocytes, reticulocytes, leukocytes, and platelets, in association with bone marrow hypocellularity, and adverse renal and gastrointestinal effects have been seen with tigecycline at exposures of 8 and 10 times the human daily dose based on AUC in rats and dogs, respectively. These alterations were shown to be reversible after two weeks of dosing.

Bone discolouring was observed in rats which was not reversible after two weeks of dosing.

Results of animal studies indicate that tigecycline crosses the placenta and is found in foetal tissues. In reproduction toxicity studies, decreased foetal weights in rats and rabbits (with associated delays in ossification) and foetal loss in rabbits have been observed with tigecycline. Tigecycline was not teratogenic in the rat or rabbit. **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.**

Results from animal studies using ^{14}C-labelled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in the nursing pups as a result of exposure via maternal milk.

Lifetime studies in animals to evaluate the carcinogenic potential of tigecycline have not been performed, but short-term genotoxicity studies of tigecycline were negative.

Bolus intravenous administration of tigecycline has been associated with a histamine response in animal studies. These effects were observed at exposures of 14 and 3 times the human daily dose based on the AUC in rats and dogs respectively.

No evidence of photosensitivity was observed in rats following administration of tigecycline.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hydrochloric acid, sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
~~Tygacil must not be mixed with other medicinal products for which compatibility data are not available (see section 6.6).~~

6.3 Shelf life

~~24 months~~ **2 years**.

Once reconstituted and diluted in the bag or other suitable infusion container (e.g. glass bottle), tigecycline should be used immediately.

6.4 Special precautions for storage

~~Store at or below~~ **Store below** 25°C.
For storage conditions of the reconstituted product see section 6.3.

6.5 Nature and contents of container

5 ml Type 1 clear glass vials fitted with grey butyl rubber stoppers and snap-off aluminium crimp seals. Tygacil is distributed in a ten vial tray pack.

6.6 Special precautions for disposal and other handling

The lyophilised 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 tigecycline. The vial should be gently swirled until the medicinal product 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.

Tygacil may 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 Tygacil 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 tigecycline and any other medicinal product(s) via this common line (see section 6.2)

This medicinal product is for single use only; any unused solution should be discarded.

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 Tygacil diluted in sodium chloride 0.9 % for injection is demonstrated with the following medicinal products 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. MARKETING AUTHORISATION HOLDER

Wyeth Europa Ltd.
Huntercombe Lane South
Taplow, Maidenhead
Berkshire, SL6 0PH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/336/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 April 2006.
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Wyeth Pharmaceuticals
New Lane
Havant
Hampshire, PO9 2NG
United Kingdom

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The Marketing Authorisation Holder (MAH) should inform all healthcare professionals who are expected to prescribe/use Tygacil about the new important identified and potential risks of the product by means of a Direct Healthcare Professional Communication (DHPC)

Within 1 month of the Commission Decision the MAH shall ensure that all healthcare professionals who are expected to prescribe/use Tygacil are invited to participate in a specific Educational Program (EP), aimed at communicating scientific information regarding the new changes in the SmPC (i.e. the new identified risk of superinfection, and the new potentials risks of lack of efficacy and off label use . The key elements of the EP should have been previously agreed with the CHMP. Final materials for the EP should be approved by National Competent Authorities according to national regulations.
~~Not applicable.~~

- **OTHER CONDITIONS**

The MAH shall perform a Post-Authorisation Study (PASS) aimed at describing how Tygacil is prescribed and monitoring superinfections and treatment outcome. For this purpose, the MAH should perform the PASS by Q2 2012 according to the final protocol agreed with the CHMP.

Pharmacovigilance system

The Marketing Authorisation Holder must ensure that the system of pharmacovigilance as described in version 3.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is placed on the market.

Risk Management Plan

The MAH commits to include the risk minimization activities identified above and the PASS in the Risk Management Plan (RMP). The new RMP should be submitted within 2 weeks of the Commission Decision.

The Marketing Authorisation Holder commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version ~~4~~ **6**.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- **When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities**
- **Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached**
- **At the request of the European Medicines Agency**

PSURs

The MAH will continue to submit yearly Periodic Safety Update Reports, unless otherwise specified by the CHMP.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tygacil 50 mg powder for solution for infusion
Tigecycline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 50 mg tigecycline.

3. LIST OF EXCIPIENTS

Each vial contains ~~100 mg of~~ lactose monohydrate. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

powder for solution for infusion
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use for directions on reconstitution and dilution.
For intravenous use after reconstitution and dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

~~Store at or below~~ **Store below** 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Wyeth Europa Ltd.
Huntercombe Lane South
Taplow, Maidenhead
Berkshire, SL6 0PH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/336/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tygacil 50 mg powder for infusion
Tigecycline
For IV use only

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET INFORMATION FOR THE USER

Tygacil 50 mg powder for solution for infusion
tigecycline

~~**Read all of this leaflet carefully before you are given this medicine.**~~
~~- Keep this leaflet. You may need to read it again.~~
~~- If you have any further questions, ask your doctor or your pharmacist.~~
~~- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.~~
~~- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.~~

Read all of this leaflet carefully before you are given this medicine.
- **Keep this leaflet. You may need to read it again.**
- **If you have any further questions, ask your doctor or your pharmacist.**
- **This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.**
- **If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.**

In this leaflet:

1. WHAT TYGACIL IS AND WHAT IT IS USED FOR

Tygacil is an antibiotic of the glycylcycline group that works by stopping the growth of bacteria that cause infections.

Your doctor prescribed Tygacil because you have one of the following types of serious infections:

- Complicated infection of the skin and soft tissues **(the tissue below the skin)**

  Tygacil is not indicated for the treatment of diabetic foot infections.

- Complicated infection in the abdomen

Tygacil should be used only in situations where it is known or suspected that other alternative antibiotics are not suitable.

2. BEFORE YOU RECEIVE TYGACIL

Do not use Tygacil
- If you are allergic (hypersensitive) to tigecycline, the active substance of Tygacil. If you are allergic to tetracycline class antibiotics (e.g., minocycline, doxycycline, etc.), you may be allergic to tigecycline.

Take special care with Tygacil

- Tell your doctor immediately if you develop symptoms of an allergic reaction.
- Tell your doctor immediately if you develop severe abdominal pain, nausea, and vomiting. These may be symptoms of acute pancreatitis.
- Tell your doctor if you are suffering from diarrhoea before you are given Tygacil. If you develop diarrhoea during or after your treatment, tell your doctor at once. Do not take any diarrhoea medicine without first checking with your doctor.
- Tell your doctor if you have or previously had any side effects due to antibiotics belonging to the tetracycline class (e.g., skin sensitization to sun light, staining on developing teeth, pancreas inflammation, and alteration of certain laboratory values aimed at measuring how well your blood clots).
- In certain serious infections, your doctor may consider to use Tygacil in combination with other antibiotics.
- Tell your doctor if you are taking certain medicines (named anticoagulants) aimed at avoiding an excess of blood clotting (see also Using other medicines in this leaflet).
- Tell your doctor if you are taking the contraceptive pill as you may need an additional method of contraception while receiving Tygacil (see also Using other medicines in this leaflet).
- Tell your doctor if you have, or previously had liver problems. Depending on the condition of your liver, your doctor may reduce the dose to avoid potential side effects.
- While antibiotics including Tygacil fight certain bacteria, other bacteria and fungi may continue to grow. This is called overgrowth. Your doctor will monitor you for any potential infections and treat you if necessary.
- Tygacil is not to be used in children or adolescents (under 18 years of age). In children less than 8 years, tigecycline may induce permanent dental defects such as staining on the developing teeth.
- **If you are given Tygacil your doctor will monitor you closely for the development of another infection. If you develop another infection your doctor may prescribe a different antibiotic.**

Using other medicines
Always tell your doctor if you are taking or have recently taken any other medicines, including medicines you buy without a prescription.

Tygacil may prolong certain tests that measure how well your blood is clotting. It is important that you tell your doctor if you are taking medicines to avoid an excess of blood clotting. If this were the case, your doctor will monitor you closely.

Tygacil may interfere with the contraceptive pill (birth control pill). Talk to your doctor about the need for an additional method of contraception while receiving Tygacil.

Pregnancy and breast-feeding
Tygacil may cause foetal harm. If you are pregnant, or are planning to become pregnant, talk to your doctor before receiving Tygacil.

It is not known if Tygacil passes into breast milk in humans. Ask your doctor for advice before breast-feeding your baby.

Driving and using machines
Tygacil may cause side effects such as dizziness. This may impair your ability to drive or operate machinery.

3. HOW TYGACIL IS GIVEN

Tygacil will be given to you by a doctor or a nurse.

The recommended dose is 100 mg given initially, followed by 50 mg every 12 hours. This dose is given intravenously (directly into your blood stream) over a period of 30 to 60 minutes.

A course of treatment usually lasts for 5 to 14 days. Your doctor will decide how long you should be treated.

If you receive more Tygacil than you should
If you are concerned that you may have been given too much Tygacil, talk to your doctor or nurse immediately.

If you miss a dose of Tygacil
If you are concerned that you may have missed a dose, talk to your doctor or nurse immediately.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Tygacil may have side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

Very common~~(affects more than 1 user in 10)~~ side effects ~~reported in at least 1 in 10 patients receiving Tygacil~~ are:

- Nausea, vomiting, diarrhoea.

Common ~~(affects 1 to 10 users in 100)~~ side effects ~~reported in at least 1 in 100 patients but in less than 1 in 10 patients receiving Tygacil~~ are:

- Abscess (collection of pus), infections
- Laboratory measurements of decreased ability to form blood clots
- Dizziness
- Vein irritations from the injection, including pain, inflammation, swelling and clotting
- Abdominal pain, dyspepsia (stomach ache and indigestion), anorexia (loss of appetite)
- Increases in liver enzymes, hyperbilirubinaemia (excess of bile pigment in the blood)
- Pruritus (itching), rash
- Headache
- Increase in amylase, which is an enzyme found in the salivary glands and pancreas, increased blood urea nitrogen (BUN).

Uncommon~~(affects 1 to 10 users in 1,000~~ side effects ~~reported in at least 1 in 1,000 patients but less than 1 in 100 patients receiving Tygacil~~ are:

- Sepsis (severe infection in the body and blood stream)/septic shock (serious medical condition which can lead to multiple organ failure and death as a result of sepsis)
- Low protein levels in the blood
- Acute pancreatitis (inflamed pancreas which may result in severe abdominal pain, nausea, and vomiting)
- Jaundice, inflammation of the liver
- Injection site reaction (pain, redness, inflammation).

~~Other side effects reported (frequency~~ **N**ot known ~~(frequency cannot be estimated from the available data)~~ **side effects** ~~in patients receiving Tygacil~~ are:

- Anaphylaxis/anaphylactoid reactions (that may range from mild to severe, including a sudden, generalised allergic reaction that may lead to a life-threatening shock [e.g. difficulty in breathing, drop of blood pressure, fast pulse]).
- Low platelet levels in the blood (which may lead to an increased bleeding tendency and bruising/haematoma)
- Liver failure

Pseudomembranous colitis may occur with most antibiotics including Tygacil. This consists of severe, persistent or bloody diarrhoea associated with abdominal pain or fever, which can be a sign of serious bowel inflammation, which may occur during or after your treatment.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TYGACIL

Keep out of the reach and sight of children.

Store below 25°C. ~~Tygacil should be stored at or below 25°C.~~
Do not use Tygacil after the expiry date which is stated on the vial.

Storage after preparation
Once the powder has been made into a solution and diluted ready for use, it should be given to you almost immediately.

6. FURTHER INFORMATION

What Tygacil contains
The active substance is tigecycline. Each vial contains 50 mg of tigecycline.

The other ingredients are lactose monohydrate, hydrochloric acid, and sodium hydroxide.

What Tygacil looks like and contents of the pack
Tygacil is supplied **as a powder for solution for infusion** in a vial and looks like an orange powder or cake before it is diluted. These vials are distributed to the hospital in a ten tray pack. The powder should be mixed in the vial with a small amount of solution. The vial should be gently swirled until the medicine is dissolved. Thereafter, the solution should be immediately withdrawn from the vial and added to a 100 ml intravenous bag or other suitable infusion container in the hospital.

The Tygacil solution should be yellow to orange in colour after dissolving; if it is not, the solution should be discarded.

Marketing Authorisation Holder:
Wyeth Europa Ltd.
Huntercombe Lane South
Taplow, Maidenhead
Berkshire, SL6 0PH
United Kingdom

Manufacturer:
Wyeth Pharmaceuticals
New Lane
Havant
Hampshire PO9 2NG
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
Luxembourg/Luxemburg
Pfizer S.A. / N.V.
Tél/Tel: +32 (0)2 554 62 11

България/Eesti/Latvija/Lietuva/
Slovenija
Wyeth Whitehall Export GmbH
Тел/Tel/Tãlr:+43 1 89 1140

Česká Republika
Pfizer s.r.o.
Tel: +420-283-004-111

Danmark
Pfizer ApS
Tlf: +45 44 201 100

Deutschland
Pfizer Pharma GmbH
Tel: +49 (0)30 550055-51000

Ελλάδα
Pfizer Hellas A.E.
Τηλ.: +30 210 6785 800

España
Pfizer, S.A.
Télf:+34914909900

France
Pfizer
Tél +33 1 58 07 30 00

Ireland
Wyeth Pharmaceuticals
Tel: +353 1 449 3500

Ísland
Icepharma hf
Tel: +354 540 8000

Italia
Wyeth Lederle S.p.A.
Tel: +39 06 927151

Κύπρος
Wyeth Hellas (Cyprus Branch) AEBE
Τηλ: +357 22 817690

Magyarország
Pfizer Kft.
Tel: +36 1 488 3700

Malta
Vivian Corporation Ltd.
Tel: +35621 344610

Nederland
Wyeth Pharmaceuticals B.V.
Tel: +31 23 567 2567

Norge
Pfizer AS
Tlf: +47 67 526 100

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.,
Tel.: +48 22 335 61 00

Portugal
Laboratórios Pfizer, Lda.
Tel: (+351) 21 423 55 00

România
Pfizer Romania S.R.L
Tel: +40 (0) 21 207 28 00

Slovenská Republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: + 421 2 3355 5500

Suomi/Finland
Pfizer Oy
Puh/Tel: +358 (0)9 430 040

Sverige
Pfizer AB
Tel: +46 (0)8 550 520 00

United Kingdom
Wyeth Pharmaceuticals
Tel: +44 1628 415330

This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

The following information is intended for medical or healthcare professionals only:

Instructions for use and handling (see also **3. HOW TYGACIL IS GIVEN** in this leaflet**)**

The lyophilised 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 tigecycline. The vial should be gently swirled until the active substance 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 for infusion 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.

Tygacil may 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 Tygacil 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 tigecycline and any other medicinal product(s) via this common line.

Compatible intravenous solutions include: sodium chloride 9 mg/ml (0.9 %) solution for injection, dextrose 50 mg/ml (5 %) solution for injection, and Lactated Ringer's solution for injection.

When administered through a Y-site, compatibility of Tygacil diluted in sodium chloride 0.9 % for injection is demonstrated with the following medicinal products 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.

Tygacil must not be mixed with other medicinal products for which compatibility data are not available.

Once reconstituted and diluted in the bag or other suitable infusion container (e.g. glass bottle) tigecycline should be used immediately.

For single use only, any unused solution should be discarded.