SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TYGEPOL 50 mg Lyophilized Powder for Solution for I.V. Infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance : Tigecycline
Each vial of TYGEPOL contains 50 mg of lyophilized tigecycline powder for intravenous infusion. After reconstitution, 1 ml contains 10 mg of tigecycline.

Excipients:
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate powder for solution for intravenous infusion, sterile
Orange lyophilized cake or powder.
Reconstituted solution is yellow or orange colored solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TYGEPOL should be used only where it is known or suspected that other alternatives are not suitable.
TYGEPOL is indicated in adults for the treatment of the following infections:

- Complicated skin and skin structure infections, including methicillin-resistant *Staphylococcus aureus* (MRSA)
- Complicated intraabdominal infections
- Community-acquired bacterial pneumonia caused by *Streptococcus pneumoniae* (penicillin-sensitive isolates), *Haemophilus influenza* (beta-lactamase negative isolates), and *Legionella pneumophila*, including cases with concurrent bacteremia.

TYGEPOL is not indicated for the treatment of diabetic foot infections (see Section 5.2).
The clinical trial to demonstrate that TYGEPOL is non-inferior in the treatment of diabetic foot infection has failed.

4.2 Posology and method of administration

Posology / frequency and duration of administration
It is administered intravenously at an initial dose of 100 mg followed by 50 mg every 12 hours.
The recommended duration of treatment for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days. The recommended duration of treatment for community-acquired bacterial pneumonia is 7 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.

Route of administration
TYGEPOL is administered by intravenous infusion. Infusions should be administered over approximately 30 to 60 minutes.

Additional information on special populations
Kidney failure
No dosage adjustment is necessary in patients with renal impairment or in patients undergoing haemodialysis (see section 5.2).

Hepatic failure
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 initial dose of TYGACIL should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment should be treated with caution and monitored for treatment response (see Section 4.4 and 5.2)

Pediatric population
TYGEPOL should not be used in children aged under 8 years because of teeth discoloration. TYGEPOL is not recommended in children younger than 18 since its safety and efficacy have not been established in this age group.

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

4.3 Contraindications
TYGEPOL is contraindicated in patients with known hypersensitivity to tigecycline or to any of the components contained in the medicine.
Patients hypersensitive to tetracycline class antibiotics may be hypersensitive to tigecycline.

4.4 Special warnings and precautions for use

An increase in all-cause mortality has been observed in Phase 3 and 4 clinical trials in tigecycline-treated patients versus comparator-treated patients. The cause of the mortality risk difference of 0.6% (95% CI, 0.1, 1.2) has not been established. TYGEPOL should be used only where it is known or suspected that other alternatives are not suitable.

In a meta-analysis of 13 Phase 3 and 4 clinical trials that included a comparator, death occurred in 4.0% (150/3788) of patients receiving tigecycline and 3.0% (110/3646) of patients receiving comparator drugs; resulting in an adjusted 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, the

adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1, 1.2) between tigecycline and comparator-treated patients. An analysis of mortality in all trials conducted for approved indications (including post-marketing trials) showed an adjusted mortality rate of 2.5% (66/2640) for tigecycline and 1.8% (48/2628) for comparator, respectively. The adjusted risk difference for mortality stratified by trial weight was 0.6% (95% CI 0.0, 1.2).

The cause of this mortality difference has not been established. Generally, deaths were the result of worsening infection, complications of infection or underlying co-morbidities. TYGEPOL should be used only where it is known or suspected that other alternatives are not suitable.

Anaphylactic reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening.

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 diarrhea during or subsequent to the administration of any antibacterial agent.

In clinical trials in patients with complicated intraabdominal infection, impaired healing of the surgical wound has been associated with superinfection. A patient developing impaired healing should be monitored for the detection of superinfection. Patients who develop superinfections, in particular nosocomial pneumonia, appear to be associated with poorer outcomes. Patients should be closely monitored for the development of superinfection. If a focus of infection other than complicated skin and soft tissue infections or complicated intra-abdominal infections is identified after initiation of TYGEPOL 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 present.

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. Hepatic failure may occur in patients treated with tigecycline due to the underlying conditions or concomitant medicinal products.

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.

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 (increased BUN, azotaemia, acidosis, and hyperphosphataemia). As with all tetracyclines, pancreatitis has been reported in association with the use of TYGEPOL. Caution should therefore be exercised in patients with hypersensitivity to tetracycline class antibiotics.

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 (58.6%), followed by major abscesses (24.9%). 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 (25.8%), peripheral vascular disease (10.4%), intravenous substance abuse (4.0%), and HIV-positive infection (1.2%). Limited experience is also available in treating patients with concurrent bacteraemia (3.4%). 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.

In clinical trials in complicated intraabdominal infections, the most common type of infection in tigecycline-treated patients was complicated appendicitis (50.3%), followed by other diagnoses less commonly reported such as complicated cholecystitis (9.6%), perforation of intestine (9.6%), intra-abdominal abscess (8.7%), gastric or duodenal ulcer perforation (8.3%), peritonitis (6.2%) and complicated diverticulitis (6.0%). Of these patients, 77.8% had surgically-apparent peritonitis. There were a limited number of patients with severe underlying disease such as immunocompromised patients, patients with APACHE II scores > 15 (3.3%), or with surgically apparent multiple intra-abdominal abscesses (11.4%). Limited experience is also available in treating patients with concurrent bacteraemia (5.6%). Therefore, caution is advised when treating such patients. Results of studies in rats with tigecycline have shown bone discolouration. TYGEPOL may be associated with permanent tooth discolouration in humans if used during tooth development.

Monotherapy with tigecycline should be avoided in patients with complicated intra-abdominal infections secondary to clinically apparent intestinal perforation. In Phase III complicated intra-abdominal infection studies (n=1642), 6 patients treated with tigecycline and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with tigecycline had higher APACHE II scores (median=13) versus the 2 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.

Increases in total bilirubin concentration, prothrombin time and transaminases have been seen in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing tigecycline therapy. Side effects may be experienced after discontinuation of the drug.

A trial of patients with hospital acquired, including ventilator-associated, pneumonia failed to demonstrate the efficacy of tigecycline. In this trial, patients were randomized to receive tigecycline (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 tigecycline had lower cure rates (47.9% versus 70.1% for the clinically evaluable population) and greater mortality (25/131 [19.1%] versus 15/122 [12.3%]) compared to the comparator-treated patients.

Particularly high mortality was seen among tigecycline-treated patients with ventilator-associated pneumonia and bacteremia at baseline (9/18 [50.0%] versus 1/13 [7.7%] in comparator-treated patients).

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including tigecycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. *difficile.*

C. *difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If pseudomembranous colitis is suspected or confirmed, ongoing antibiotic use not directed against C. *difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. *difficile*, and surgical evaluation should be instituted as clinically indicated.

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 secondary to clinically apparent intestinal perforation or patients with incipient sepsis or septic shock.

Prothrombin time or other suitable anticoagulation test should be used to monitor patients if tigecycline is administered with anticoagulants.
This medicinal product contains less than 1 mmol (23 mg) sodium per ml, i.e. it is essentially "sodium free". No adverse affect associated with sodium is expected.

4.5 Interactions with other medical products and other forms of interaction
Interaction studies have only been performed in adults.

In a drug interaction study, tigecycline (100 mg followed by 50 mg every 12 hours) and digoxin (0.5 mg followed by 0.25 mg every 24 hours) were administered to healthy volunteers. Tigecycline caused a slight (13%) decrease in C_{max} of digoxin but did not have any impact on the AUC (area under curve) or clearance. This small change in C_{max} did not change the steady-state pharmacodynamics of digoxin, as evidenced by changes in ECG interval measurements. 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.

Concomitant administration of tigecycline (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 C_{max} by 38% and 43% and in AUC by 68 % and 29 %, respectively. The mechanism of this interaction is still not elucidated.
Tigecycline did not result in significant INR (International normalized ratio, PT) changes. Warfarin did not affect the pharmacokinetic profile of tigecycline.

In cases where tigecycline is administered with warfarin, monitoring with prothrombin time or another suitable anticoagulation test may be appropriate. Warfarin did not affect the pharmacokinetic profile of tigecycline.

In vitro studies with human liver microsomes have shown that the metabolism of cytochrome P450 (CYP) isoforms via 1A2, 2C8, 2C9, 2C19, 2D6 and 3A4 is not inhibited by tigecycline. For this reason, tigecycline is not expected to change the metabolism of other drugs metabolised by these enzymes.

In addition, tigecycline is not extensively metabolised. Therefore, clearance of tigecycline is not expected to be affected by drugs that inhibit or induce these isoforms. In vitro, tigecycline is neither a competitive inhibitor nor an irreversible inhibitor of CYP450 enzymes.

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

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

Based on an in vitro study tigecycline is a P-gp substrate. Co-administration of P-gp inhibitors (e.g., ketoconazole or cyclosporine) or P-gp inducers (e.g., rifampicin) could affect the pharmacokinetics of tigecycline.

Additional information on special populations
No clinical interaction study has been performed in special populations.

Pediatric population:
No interaction study has been performed in pediatric populations.

4.6 Pregnancy and lactation
General recommendation
Pregnancy category: D

Women with childbearing potential/Contraception:
Women with childbearing potential should use an adequate and effective birth control method.
Concurrent use of antibiotics with oral contraceptives may render oral contraceptives less effective.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. The results of animal experiments **indicate that tigecycline may be harmful to the fetus if administered in pregnancy.** 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 fetuses, 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. Tigecycline should not be used during pregnancy unless the clinical condition of the woman requires treatment with tigecycline.

Tigecycline has not been investigated for prenatal and postnatal use. TYGEPOL should not be used in pregnancy unless required.

Lactation
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tigecycline is administered to a nursing woman.
Care should be taken during treatment with tigecycline to consider stopping breastfeeding as the potential risk in breast-fed infants cannot be excluded.

Fertility
Tigecycline did not affect mating or fertility in rats at exposures up to 4.7 times the human daily dose based on AUC (area under curve). In female rats, there were no compound-related

effects on ovaries or oestrus cycles at exposures to tigecycline at the same doses. There is no adequate information on fertility in humans.

4.7 Effects on ability to drive and use machines

No studies on the effects of tigecycline on the ability to drive or use machines have been performed. TYGEPOL may cause dizziness and may have an effect on driving and use of machines.

4.8 Undesirable effects

The total number of patients with complicated skin and soft tissue infections and complicated intra-abdominal infections treated with tigecycline in Phase 3 and 4 clinical studies was 2,393.

In clinical trials, the most common medicinal product-related treatment emergent adverse reactions were reversible nausea (21%) and vomiting (13%). These side effects usually occurred early (on treatment days 1-2) and were generally mild or moderate in severity.

Adverse reactions reported with tigecycline, including clinical trials and post-marketing experience, are tabulated below.

Undesirable effects are listed according to the following categories: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1000 to < 1/100); Rare (≥ 1/10000 to < 1/1000); Very rare (< 1/10000); Not known (cannot be estimated from the available data)

Post-marketing experience with Tigecycline is obtained from spontaneous reports and its frequency is unpredictable. So they are classified as not known.

Infections and Infestations:

Common: Pneumonia, abscess, infections, sepsis/septic shock

Blood and lymphatic system disorders:

Common: prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time (PT)

Uncommon: Thrombocytopenia, increased international normalized ratio (INR)

Immune system disorders:

Not known: Anaphylaxis/ anaphylactoid reactions *(See section 4.3 and 4.4)*

Metabolism and nutrition disorders:

Common: Bilirubinemia, hypoglycemia, hyperproteinemia

Nervous system disorders:

Common: Dizziness

Vascular disorders:
Common: Phlebitis
Uncommon: Thrombophlebitis

Gastrointestinal disorders
Very common: Nausea, vomiting, diarrhea
Common: Abdominal pain, dyspepsia, anorexia
Uncommon: Acute pancreatitis

Hepatobiliary Disorders:
Common: Elevated serum aspartate aminotransferase (AST) and elevated serum alanine aminotransferase (ALT), hyperbilirubinemia
Uncommon: Jaundice, liver injury (mostly cholestatic)
Not known: Hepatic failure (see section 4.4)

Skin and subcutaneous tissue disorders:
Common: Pruritus, rash
Not known: Severe skin reactions, including Stevens-Johnson Syndrome

General disorders and administration site conditions:
Common: Headache, impaired healing, injection site reactions
Uncommon: Injection site inflammation, injection site pain, edema and phlebitis.
Investigations:
Common: Elevated serum amylase, increased blood urea nitrogen (BUN)

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 hyperphosphatasemia *(see section 4.4)*.

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

In Phase 3 and 4 clinical trials on complicated skin and soft tissue infections and complicated intra-abdominal infections, infection-related serious adverse reactions were more frequently reported for subjects treated with tigecycline (7.1%) vs comparators (5.3%). Significant

differences in sepsis/septic shock with tigecycline (2.2%) vs comparators (1.1%) were observed.

AST and ALT abnormalities in tigecycline-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 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of patients receiving tigecycline and 3.0% (110/3646) of patients receiving comparator drugs. In a meta-analysis of these trials, an adjusted risk difference of all-cause mortality was 0.9% (95% CI 0.1, 1.8) between tigecycline and comparator-treated patients.

In a pooled analysis of these trials, based on a random effects model by trial weight, the adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1, 1.2) between tigecycline and comparator-treated patients.

No significant difference was observed between tigecycline and the comparator in terms of the infection type. The cause of the imbalance has not been established. Generally, deaths were the result of worsening infection, complications of infection or underlying co-morbidities.

The most common adverse reactions requiring immediate treatment were nausea and vomiting with an incidence of 26% (17% mild, 8% moderate, 1% severe) and 18% (11% mild, 6% moderate, 1% severe), respectively. Nausea and vomiting generally occurred during the first 1 – 2 days of therapy.

Additional information on special populations

Pediatric population
Very limited safety data were available from multiple dose pharmacokinetic (PK) studies. No new or unexpected safety concerns were observed with tigecycline in these studies.

4.9 Overdose and therapy
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: Antibacterial for systemic use, tetracycline
ATC Code: J01AA12

Mechanism of action
Tigecycline, a glycylcycline antibiotic, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. Tigecycline carries a glycylamido moiety attached to the 9-position of minocycline. The substitution pattern is not present in any naturally occurring or semisynthetic tetracycline and imparts certain microbiologic properties to tigecycline. Tigecycline is not affected by the two major tetracycline resistance mechanisms, ribosomal protection and efflux. Accordingly, tigecycline has demonstrated in vitro and in vivo activity against a broad spectrum of bacterial pathogens. Cross-resistance between tigecycline and minocycline-resistant isolates among the *Enterobacteriaceae* due to multi-drug resistance (MDR) efflux pumps has been shown.

There has been no cross resistance observed between tigecycline and other antibiotics. In vitro studies have not demonstrated antagonism between tigecycline and other commonly used antibacterial drugs.

Tigecycline is vulnerable to chromosomally-encoded multi-drug efflux pumps of *Proteeae* and *Pseudomonas aeruginosa*. Pathogens of the family *Proteeae* (*Proteus spp., Providencia spp.*, and *Morganella spp*.) are generally less susceptible to tigecycline than other members of the *Enterobacteriaceae*. Decreased susceptibility in both groups has been attributed to the overexpression of the non-specific AcrAB multi-drug efflux pump. Decreased susceptibility in Acinetobacter baumannii has been attributed to the overexpression of the AdeABC efflux pump.

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*. Partial bactericidal activity and a 3-log reduction was observed with tigecycline against *Neisseria gonorrhoeae*.

Tigecycline has also shown bactericidal action against common respiratory tract strains such as *S. pneumoniae, H. influenzae* and *L. pneumophila*.

Where possible, the clinical microbiology laboratory should provide periodic reports describing the cumulative in vitro susceptibility test results of antimicrobial drugs used in local hospitals and application areas, and the susceptibility profile of nosocomial and community pathogens. These reports will assist physicians in selecting the most effective antimicrobial medication.
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. The following information is an estimated guideline for determining whether microorganisms are susceptible to tigecycline:

Pathogen
Gram-positive Aerobes
Enterococcus spp.[+]
*Staphylococcus aureus**
Staphylococcus epidermidis
Staphylococcus haemolyticus
*Streptococcus agalactiae**
*Streptococcus anginosus** (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.

Serratia marcescens *Stenotrophomonas maltophilia* **Aerobes** *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.

Cardiac Electrophysiology
In 46 healthy volunteers in a randomized, placebo and active, controlled four-arm cross QTc study, significant effect of a single intravenous dose of tigecycline of 50 mg or 200 mg on the QTc interval was not observed.

Pediatric population
In an open-label, increasing multidose study, to 39 children aged between 8 and 11 with KİAE or kDYDE, tigecycline (0.75, 1 or 1.25 mg/kg) was administered. Up to 14 consecutive days,
all patients took at least 3 consecutive days with the option of switching to oral antibiotics on 4th day or afterwards, they took IV tigecycline.
Clinical improvement was evaluated 10 and 21 days after the last dose administered.
Here is a summary of the clinical response in the modified therapeutic (mITT) population results:

Clinical Treatment/mITT population			
	0.75 mg/kg	1 mg/kg	1.25 mg/kg
Indıcation	n/N (%)	n/N (%)	n/N (%)
kİAE	6/6 (100.0)	3/6 (50.0)	10/12 (83.3)
kDYDE	3/4 (75.0)	5/7 (71.4)	2/4 (50.0)
General	9/10 (90.0)	8/13 (62.0)	12/16 (75.0)

Since there are other antibiotics used together in this study, the efficacy data shown must be carefully examined. In addition, few patients should be taken into account.

Resistance
Resistance was found rarely in strains determined to be sensitive to tigecycline in European surveillance studies. There is no target-based cross-resistance between tigecycline and most classes of antibiotics. Tigecycline is able to overcome the two major tetracycline resistance mechanisms, ribosomal protection and efflux. In *in vitro* studies, no antagonism has been observed between tigecycline and other antibiotic classes.

Clinical efficacy and safety

Complicated Skin and Skin Structure Infections

Tigecycline was evaluated in adults for the treatment of complicated skin and skin structure infections (cSSSI) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 300 and 305). These studies compared tigecycline (100 mg intravenous initial dose followed by 50 mg every 12 hours) with vancomycin (1 g intravenous every 12 hours)/aztreonam (2 g intravenous every 12 hours) for 5 to 14 days. Patients with complicated deep soft tissue infections including wound infections and cellulitis (≥10 cm, requiring surgery/drainage or with complicated underlying disease), major abscesses, infected ulcers, and burns were enrolled in the studies. The primary efficacy endpoint was the clinical response at the test of cure (TOC) visit in the co-primary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) patients. (See TABLE 1) Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in table below.

Table 1: Clinical Cure Rates from Two Studies in Complicated Skin and Skin Structure Infections after 5 to 14 Days of Therapy

	Tigecycline[a] n/N(%)	Vancomycin/Aztreonam[b] n/N (%)
Study 300		
CE	165/199 (82,9)	163/198 (82,3)
c-mITT	209/277 (75,5)	200/260 (76,9)
Study 305		
CE	200/223 (89,7)	201/213 (94,4)
c-mITT	220/261 (84,3)	225/259 (86,9)

[a] 100 mg initially, followed by 50 mg every 12 hours

[b] Vancomycin (1 g every 12 hours)/Aztreonam (2 g every 12 hours)

Tigecycline did not meet the equivalence criterion in the study with ertapenum in patients with diabetic foot infections.

Complicated intra-abdominal infections:

Tigecycline was evaluated in adults for the treatment of complicated intraabdominal infections (cIAI) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 301 and 306). These studies compared tigecycline (100 mg intravenous initial dose followed by 50 mg every 12 hours) with imipenem/cilastatin (500 mg intravenous every 6 hours) for 5 to 14 days. Patients with complicated diagnoses including appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis were enrolled in the studies. The primary efficacy endpoint was the clinical response at the TOC visit for the co-primary populations of the microbiologically evaluable (ME) and the microbiologic modified intent-to-treat (m-

mITT) patients. (*See Table 2*) Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table below.

Table 2: Clinical Cure Rates from Two Pivotal Studies in Complicated Intra-abdominal Infections after 5 to 14 Days of Therapy

	Tigecycline[a] n/N(%)	Imipenem /Cilastatin[b] n/N (%)
Study 301		
ME	199/247 (80,6)	210/255 (82,4)
m-mITT	227/309 (73,5)	244/312 (78,2)
Study 306		
ME	242/265 (91,3)	232/258 (89,9)
m-mITT	279/322 (86,6)	270/319 (84,6)

[a] 100 mg initially, followed by 50 mg every 12 hours

[b] Imipenem/Cilastin (500 mg every 6 hours)

Community-Acquired Bacterial Pneumonia

Tigecycline was evaluated in adults for the treatment of community-acquired bacterial pneumonia (CABP) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 308 and 313). These studies compared tigecycline (100 mg intravenous initial dose followed by 50 mg every 12 hours) with levofloxacin (500 mg intravenous every 12 or 24 hours). In one study (Study 308), after at least 3 days of intravenous therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms. Total therapy was 7 to 14 days. Patients with community-acquired bacterial pneumonia who required hospitalization and intravenous therapy were enrolled in the studies. The primary efficacy endpoint was the clinical response at the test of cure (TOC) visit in the co-primary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) patients. (*See Table 2*) Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 3.

Table 3: Clinical Cure Rates from Two Studies in Community-Acquired Bacterial Pneumonia after 7 to 14 Days of Total Therapy

	Tigecycline[a] n/N(%)	Levofloxacin[b] n/N(%)	95% CI[c]
Study 308[d]			
CE	125/138 (90,6)	136/156(87.2)	(-4,4, 11,2)
c-mITT	149/191 (78)	158/203(77.8)	(-8,5, 8,9)
Study 313			
CE	128/144 (88,9)	116/136(85.3)	(-5,0, 12,2)
c-mITT	170/203 (83,7)	163/200(81.5)	(-5,6, 10,1)

[a] 100 mg initially, followed by 50 mg every 12 hours

[b] Levofloxacin (500 mg I.V. every 12 or 24 hours)

[c] 95% confidence interval for the treatment difference

[d] After at least 3 days of intravenous therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms in Study 308.

To further evaluate the treatment effect of tigecycline, a post-hoc analysis was conducted in patients with Community-Acquired Bacterial Pneumonia a higher risk of mortality, for whom the treatment effect of antibiotics is supported by historical evidence. The higher-risk group included patients with Community-Acquired Bacterial Pneumonia from the two studies with any of the following factors:

- Age ≥50 years
- PSI score ≥3
- Streptococcus pneumonia bacteremia

The results of this analysis are shown in Table 4. Age ≥50 was the most common risk factor in the higher-risk group.

Table 4: Post-hoc Analysis of Clinical Cure Rates in Patients with Community-Acquired Bacterial Pneumonia Based on Risk of Mortality[a]

	Tigecycline[a] n/N(%)	Levofloxacin n/N(%)	95% CI[b]
Study 308[c]			
CE			
High risk			
Yes	93/103 (90.3)	84/102 (82.4)	(-2,3, 18,2)
No	32/35 (91.4)	52/54 (96.3)	(-20,8, 7,1)
c-Mitt			
High risk			
Yes	111/142 (78.2)	100/134 (74.6)	(-6,9, 14)
No	38/49 (77.6)	58/69 (84.1)	(-22,8, 8.7)
Study 313			
CE			
High risk			
Yes	95/107 (88.8)	68/85 (80)	(-2,2, 20.3)
No	33/37 (89.2)	48/51 (94.1)	(-21,1, 8.6)
c-mITT			
High risk			
Yes	112/134 (83.6)	93/120 (77.5)	(-4,2, 16.4)
No	58/69 (84.1)	70/80 (87.5)	(-16,2, 8.8)

[a] Patients at higher risk of death include patients with any one of the following: ≥50 year of age; PSI score ≥3; or bacteremia due to Streptococcus pneumoniae

[b] 95% confidence interval for the treatment difference

[c] After at least 3 days of intravenous therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms in Study 308.

5.2 Pharmacokinetic properties

General properties:

Absorption:
Tigecycline is administered intravenously and therefore has 100% bioavailability.

Distribution:
The *in vitro* plasma protein binding of tigecycline ranges from approximately 71% to 89% at concentrations observed in clinical studies (0.1 to 1.0 mcg/ml). Animal and human pharmacokinetic studies have demonstrated that tigecycline readily distributes to tissues.

In rats receiving single or multiple doses of ^{14}C-tigecycline, radioactivity was well distributed to most tissues, with the highest overall exposure observed in bone marrow, salivary glands, thyroid gland, spleen, and kidney. In humans, the steady-state volume of distribution of tigecycline averaged 500 to 700 L (7 to 9 L/kg), indicating that tigecycline is extensively distributed beyond the plasma volume and concentrates into tissues.

No data are available on whether tigecycline can cross the blood-brain barrier in humans.
In clinical pharmacology studies using the therapeutic dosage regimen of 100 mg followed by 50 mg every 12 hours, 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. Two separate studies examined the steady-state pharmacokinetic profile of tigecycline in specific tissues or fluids of healthy subjects. In a bronchoalveolar lavage study, the Area under Curve concentration of tigecycline (AUC_{0-12h}) of 134 mcg·hr/mL in alveolar cells was 78-fold higher than the AUC_{0-12h} in the serum of these subjects.

In the same study, the AUC_{0-12h} (2.28 mcg·hr/mL) in epithelial lining fluid was 32% higher than the AUC_{0-12} in serum. In a skin blister study, the AUC_{0-12h} (1.61 mcg·hr/mL) of tigecycline in skin blister fluid was approximately 26% lower than the AUC_{0-12h} 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.

Biotransformation

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 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.
In healthy male volunteers receiving ^{14}C-tigecycline, tigecycline was the primary ^{14}C-labeled material recovered in urine and feces, 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 feces and urine following administration of ^{14}C-tigecycline indicates that 59% of the dose is eliminated by biliary/fecal 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.

Tigecycline is a substrate of P-gp based on an in vitro study using a cell line overexpressing P-gp. The potential contribution of P-gp-mediated transport to the in vivo disposition of tigecycline is not known. Co-administration of P-gp inhibitors (e.g., ketoconazole or cyclosporine) or P-gp inducers (e.g., rifampicin) could affect the pharmacokinetics of tigecycline.

Linearity / Non-linearity:
Tigecycline has linear pharmacokinetic properties.

Special Populations
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).

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) (see section 4.2).

Renal failure:

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.

Geriatric population:
No overall differences in pharmacokinetics were observed between healthy elderly subjects and younger subjects.

Pediatric patients:
Tigecycline pharmacokinetics have not been established in children aged 8-18 years.
Tigecycline pharmacokinetics was investigated in two studies. The first study enrolled children aged 8-16 years (n=24) who received single doses of tigecycline (0.5, 1, or 2 mg/kg, without dose limitation) administered intravenously over 30 minutes. The second study was performed in children aged 8 to 11 years who received multiple doses of tigecycline (0.75, 1, or 1.25 mg/kg up to a maximum dose of 50 mg) every 12 hours administered intravenously over 30 minutes. Pharmacokinetic parameters observed are given below.

Mean dose normalized to 1 mg / kg in children ± SD tigecycline C_{max} and AUC			
Age (years)	N	C_{max}(ng/ml)	AUC (ng.h/mL)*
Single dose			
8-11	8	3881±6637	4034±2874
12-16	16	8508±11433	7026±4088
Multiple dose			
8-11	42	1911±3032	2404±1000

*single dose $AUC_{0-\infty}$, multiple dose AUC_{0-12s}
The target AUC_{0-12h} in adults after the recommended dose of 100 mg loading and 50 mg every 12 hours, was approximately 2500 ng•h/mL.

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-normalized clearance, and AUC were not appreciably different among patients with different body weights, including those 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 fetal tissues. In reproduction toxicity studies, decreased fetal weights in rats and rabbits (with associated delays in ossification) and fetal 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.
Tigecycline is not teratogenic in rabbits and rats. Results of animal studies indicate that ^{14}C-labelled tigecycline crosses the placenta and is found in foetal tissues. Decreased fetal weights and increased incidence of minor skeletal anomalies in rats and rabbits (with associated delays in ossification) have been observed with tigecycline administered 5 times and 1 time the human daily dose based on AUC (28 mcg·hr/mL and 6 mcg·hr/mL at 12 and 4 mg/kg/day) respectively. An increase in the incidence of fetal loss in rabbits at maternatoxic doses was observed when administered in equal doses to human doses.

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

Carcinogenicity
Lifetime studies in animals to evaluate the carcinogenic potential of tigecycline have not been performed.

Mutagenicity
No mutagenic or clastogenic potential was found in a range of in vitro assays including chromosome aberration assay in Chinese Hamster Ovary (CHO) cells, forward mutation assay in CHO cells (HGRPT locus), in vitro forward mutation assays in mouse lymphoma cells and in vivo micronucleus assay.

Bolus intravenous administration of tigecycline has been associated histamine release in animal studies. These effects occurred in rats and dogs, respectively, at doses of 14 and 3 times the daily doses in human.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Maltose
Water for injection
Hydrochloric Acid

Sodium hydroxide

6.2 Incompatibilities

The following drugs should not be administered simultaneously through the same Y-site as TYGEPOL: amphotericin B, amphotericin B lipid complex, diazepam, esomeprazole, omeprazole.

Compatible intravenous solutions are: 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 with sodium chloride 0.9% for injection (USP) or 5% dextrose solution (USP), TYGEPOL may be given through the same Y-site 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 HCl, propofol, ranitidine HCl, theophylline.

6.3 Shelf Life

24 months

6.4 Special precautions for storage

Store at room temperature below 25ºC.

The reconstituted solution should be yellow to orange in colour; if not, the solution should be discarded.

Once reconstituted, tigecycline may be stored at room temperature (25°C) for up to 24 hours (up to 6 hours in the vial and the remaining 18 hours in the intravenous bag).

Alternatively, tigecycline mixed with 9 mg/ml (0.9%) Sodium Chloride solution or 50 mg/ml (5%) Dextrose Solution may be stored refrigerated at 2° to 8°C for up to 48 hours following immediate transfer of the reconstituted solution into the intravenous bag.

Any unused solution must be discarded

6.5 Nature and contents of container

Colorless Type I glass vial.

Presented in packaging of 10 vials.

6.6 Special precautions for disposal and other handling

Instructions for administration:

Lyophilized powder should be reconstituted with 5.3 mL of 9 mg/ml (0.9%) Sodium Chloride Solution for Injection or 50 mg/ml (5%) Dextrose Solution for Injection or Lactated Ringer's Injection to achieve a concentration of 10 mg/mL of tigecycline. The vial should be gently swirled until the drug dissolves. Withdraw 5 mL of the reconstituted solution from the vial and transfer into to a 100 mL intravenous bag for infusion. For a 100 mg dose, reconstitute two vials and transfer in 100 ml I.V bag. (Note: Each 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 color; if not, the solution should be discarded.** Parenteral

drug products should be inspected visually for particulate matter and discoloration (e.g., green or black) prior to administration. Once reconstituted may be stored at room temperature for up to 24 hours (up to 6 hours in the vial and the remaining time in the intravenous bag). Alternatively, tigecycline mixed with 9 mg/ml (0.9%) Sodium Chloride solution or 50 mg/ml (5%) Dextrose Solution may be stored refrigerated at 2° C to 8°C for up to 48 hours following immediate transfer of the reconstituted solution into the intravenous bag.

Shake/swirl until product is completely dissolved during reconstitution.
TYGEPOL may be administered intravenously through a dedicated I.V line or 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 TYGEPOL with 9 mg/ml (0.9%) Sodium Chloride Solution for Injection or 50 mg/ml (5%) Dextrose Solution for Injection. Injection should be made with an infusion solution compatible with tigecycline and with any other drug(s) administered via this common line. *(See Section 6.2)*

Tigecycline is a broad-spectrum antibiotic used intravenously for empirical treatment of moderate-to-severe bacterial infections. It does not create a direct risk to the environment. Following approval, it will be distributed for administration by injection in EU countries and other European countries. The main users of the product will be hospitals and clinics. The product will be presented in vial. Each vial will contain 53 mg tigecycline lyophilized powder with 6% overage over label claim. No other excipients is present in the product. The packaging material used is suitable for distribution of this active substance as explained in our file; does not contain hazardous substances for health and the environment.

Do not throw away drugs that have expired or are not used! Deliver to the collection system determined by the Ministry of Environment and Urbanism.

7. MARKETING AUTHORISATION HOLDER
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