Tygin

1. Name of the medicinal product

Tygin 50 mg powder for solution for infusion

2. Qualitative and quantitative composition

Each 5 mL Tygin vial contains 50 mg of tigecycline. After reconstitution, 1 mL contains 10 mg of tigecycline. The product does not contain preservatives. For the full list of excipients *[see section 6.1 List of excipients]*.

3. Pharmaceutical form

Powder for solution for infusion. Orange powder.

4. Clinical particulars

4.1 Therapeutic indication

- Complicated Skin and Skin Structure Infections (cSSSI)

  Tygin is indicated in patients 18 years of age an older for the treatment of complicated skin and skin structure infections caused by susceptible isolates of *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis.*

- Complicated Intra-abdominal Infections (cIAI)

  Tygin is indicated in patients 18 years of age and older for the treatment of complicated intra-abdominal infections caused by susceptible isolates of *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.

- Community-Acquired Bacterial Pneumonia (CAP)

  Tygin is indicated in patients 18 years of age and older for the treatment of community-acquired pneumonia caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* (methicillin-susceptible isolates), *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia *Mycoplasma pneumonia*, *Chlamydia pneumoniae*, and *Legionella pneumophila*.

Tygin is not indicated for the treatment of diabetic foot infections. A clinical trial failed to demonstrate non-inferiority of Tygin for treatment of diabetic foot infections.

Tygin is not indicated for the treatment of hospital-acquired or ventilator-associated pneumonia. In a comparative clinical trial greater mortality and decreased efficacy were reported in tigecycline injection-treated patients *[see 4.4 Special warnings and precautions for use]*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Tygin and other antibacterial drugs, Tygin should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to tigecycline. Tygin may be initiated as empiric monotherapy before results of these tests are known.

4.2 Posology and method of administration

Posology

Recommended Adult Dosage

The recommended dosage regimen for tigecycline is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous infusions of tigecycline should be administered over approximately 30 to 60 minutes every 12 hours.

The recommended duration of treatment with tigecycline for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days. The recommended duration of treatment with tigecycline 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.

Dosage in Patients with Hepatic Impairment

No dosage adjustment is warranted in patients (including pediatrics) 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 tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severs hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response.

Dosage in Pediatric Patients

The safety and efficacy of the proposed pediatric dosing regimens have not been evaluated due to the observed increase in mortality associated with tigecycline in adult patients. Avoid use of tigecycline in pediatric patients unless no alternative antibacterial drugs are available. Under these circumstances, the following doses are suggested:

- Pediatric patients aged 8 to 11 years should receive 1.2 mg/kg of tigecycline every 12 hours intravenously to a maximum dose of 50 mg of tigecycline every 12 hours.
- Pediatric patients aged 12 to 17 years should receive 50 mg of tigecycline every 12 hours.

The proposed pediatric doses of tigecycline were chosen based on exposures observed in pharmacokinetic trials, which included small numbers of pediatric patients.

Monitoring of Blood Coagulation Parameters

Obtain baseline blood coagulation parameters, including fibrinogen, and continue to monitor regularly treatment with tigecycline.

Method of administration

Each vial of Tygin should be reconstituted with 5.3 mL of 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, or Lactated Ringer's Injection, USP to achieve a concentration of 10 mg/mL of tigecycline. (Note: Each vial contains a 6% overage. Thus, 5 mL of reconstituted solution is equivalent to 50 mg of the drug.) The vial should be gently swirled until the drug dissolves. Reconstitutes solution must be transferred and further diluted for intravenous infusion. Withdraw 5 ml of the reconstituted solutions from the vial and add to a 100 mL intravenous container for infusion (for a 100 mg dose, reconstitute two vials; for a 50 mg dose, reconstitute one vial). The maximum concentration in the intravenous container should be 1 mg/mL. 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, Tygin may be stored at room temperature (store below 30^{o}C) for up to 6 hours in the vial. After dilution, Tygin mixed with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP may be stored refrigerated at 2^{o} to 8^{o}C for up to 48 hours or store below 30^{o}C for up to 24 hours following transfer of the reconstituted solution into the intravenous container, such as polyethylene and polypropylene container.

Tygin 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 drugs, the line should be flushed before and after infusion of Tygin with 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP or Lactated Ringer's Injection, USP. Injection should be made with an infusion solution compatible with tigecycline and with any other drug(s) administered via this common line.

Drug Compatibilities

Compatibilities intravenous solution include 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, and Lactated Ringer's Injection, USP. When administered through a Y-site, tigecycline is compatible with the following drugs or diluents when used with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP: 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.

Drug Incompatibilities

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

4.3 Contraindications

Tygin is contraindicated for use in patients who have known hypersensitivity to tigecycline. Reactions have included anaphylactic reaction.

4.4 Special warnings and precautions for use

All-Cause Mortality: An increase in all-cause mortality has been observed in a meta-analysis of Phase 3 and 4 clinical trials in tigecycline treated patients versus comparator-treated patients. 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 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 (cSSSI, cIAI, and CABP), including post-market 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. Tigecycline should be reserved for use in situations when alternative treatments are not suitable.

Mortality Imbalance and Lower Cure Rates in Hospital-Acquired Pneumonia: 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 rated (47.9% versus 70.1% for the clinically evaluable population).

In this trial, greater mortality was seen in patients with ventilator-associated pneumonia who received tigecycline (25/131 [19.1%] versus 15/122 [12.3%] in 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).

Anaphylactic Reactions: Anaphylactic reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening. Tigecycline is structurally similar to tetracycline-class antibacterial drugs and should be avoided in patients with known hypersensitivity to tetracycline-class antibacterial drugs.

Hepatic Adverse Effects: 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. Hepatic dysfunction may occur after the drug has been discontinued.

Pancreatitis: Acute pancreatitis, including fatal cases, has occurred in association with tigecycline treatment. The diagnosis of acute pancreatitis should be considered in patients taking tigecycline who develop clinical symptoms, signs, or laboratory abnormalities suggestive of acute pancreatitis. Cases have been reported in patients without known risk factors for pancreatitis. Patients usually improve after tigecycline discontinuation. Consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis.

Monitoring of Blood Coagulation Parameters: Hypofibrinogenemia has been reported in patients treated with tigecycline. Obtain baseline blood coagulation parameters, including fibrinogen, and continue to monitor regularly during treatment with tigecycline.

Tooth Discoloration and Enamel Hypoplasia: The use of tigecycline during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of tetracyclines, but is has

been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Advise the patients of the potential risk to the fetus if tigecycline is used during the second or third trimester of pregnancy.

Inhibition of Bone Growth: The use of tigecycline during the second and third trimester of pregnancy, infancy and childhood up to the age of 8 years may cause reversible inhibition of bone growth. All tetracyclines from a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the tetracycline was discontinued. Advise the patient of the potential risk to the fetus if tigecycline is used during the second or third trimester of pregnancy.

***Clostridium difficile*-Associated Diarrhea**: *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 CDAD 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.

Sepsis/Septic Shock in Patients with Intestinal Perforation: Monotherapy with tigecycline should be avoided in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In cIAI 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.

Tetracycline-Class Adverse Effects: Tigecycline is structurally similar to tetracycline-class antibacterial drugs and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia).

Development of Drug-Resistant Bacteria: Prescribing tigecycline in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

4.5 Interaction with other medicinal products and other forms of interaction

Warfarin: Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin.

Calcineurin Inhibitors: Concomitant use of tigecycline and calcineurin inhibitors such as tacrolimus or cyclosporine may lead to an increase in serum trough concentrations of the calcineurin inhibitors. Therefore, serum concentrations of the calcineurin inhibitor should be monitored during treatment with tigecycline to avoid drug toxicity.

Oral contraceptives: Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.

4.6 Fertility, pregnancy and lactation

Pregnancy: Tigecycline, like other tetracycline class antibacterial drugs, may cause permanent discoloration of deciduous teeth and reversible inhibition of bone growth when administered during the second and third trimester of pregnancy. There are no available data on the risk of major birth defects or miscarriage following the use of tigecycline during pregnancy. Administration of intravenous tigecycline in pregnant rats and rabbits during the period of organogenesis was associated with reduction in fetal weights and an increased incidence of skeletal anomalies (delays in bone ossification) at exposures of 5 and 1 times the human exposure at the recommended clinical dose in rats and rabbits, respectively. Advise the patient of the patient of the potential risk to the fetus if tigecycline is used during the second or third trimester.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Human Data

The use of tetracycline-class antibacterial drugs, that includes tigecycline, during tooth development (second and third trimester of pregnancy) may cause permanent discoloration of deciduous teeth. This adverse reaction is more common during long-term use of tetracyclines but has been observed following repeated short-term course. Tigecycline may cause reversible inhibition of bone growth when administered during the second and third trimesters of pregnancy. A decrease in fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every 6 hours.

Animal Data

In embryo-fetal development studies, tigecycline was administered during the period of organogenesis at doses up to 12 mg/kg/day in rats and 4 mg/kg in rabbits or 5 and 1 times the systemic exposure at the recommended clinical dose, respectively. In the rat study, decreased fetal weight and fetal skeletal variations (reduced ossification of the pubic, ischial, and supraoccipital bones and increased incidences of rudimentary 14^{th} rib) were observed in the presence of maternal toxicity at 12mg/kg/day (5 times the recommended clinical dose based on systemic exposure). In rabbits, decreased fetal weights were observed in the presence of maternal toxicity 4 mg/kg (equivalent to the human exposure at the recommended clinical dose).

In preclinical safety studies, ^{14}C-labeled tigecycline crossed the placenta and was found in fetal tissues.

Lactation: There are no data on the presence of tigecycline in human milk; however, tetracycline-class antibacterial drugs are present in breast milk. It is not known whether tigecycline has an effect on the breastfed infant or on milk production. Tigecycline has low oral bioavailability; therefore, infant exposure is expected to be low. Tigecycline is present in rat milk with little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

4.7 Effects on ability to drive and use machines

Dizziness may occur and this may have an effect on driving and use of machines.

4.8 Undesirable effects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, 2514 patients were treated with tigecycline. Tigecycline was discontinued due to adverse reactions in 7% of patients compared to 6% for all comparators. Table 1 shows the incidence of treatment-emergent adverse reactions through test of cure reported in ≥2% of patients in these trials.

Table 1 Incidence (%) of Adverse reactions through test of cure reported in ≥ 2% of patients treated in clinical studies

Body system Adverse reactions	Tigecycline (N=2514)	Comparators[a] (N=2307)
Body as a Whole		
Abdominal pain	6	4
Abscess	2	2
Asthenia	3	2
Headache	6	7
Infection	7	5
Cardiovascular System		
Phlebitis	3	4
Digestive System		
Diarrhea	12	11
Dyspepsia	2	2
Nausea	26	13
Vomiting	18	9
Hemic and Lymphatic System		
Anemia	5	6
Metabolic and Nutritional		
Alkaline Phosphatase Increased	3	3
Amylase Increased	3	2
Bilirubinemia	2	1
BUN Increased	3	1
Healing Abnormal	3	2
Hyponatremia	2	1
Hypoproteinemia	5	3
SGOT Increased[b]	4	5
SGPT Increased[b]	5	5
Respiratory System		
Pneumonia	2	2
Nervous system		
Dizziness	3	3
Skin and appendages		
Rash	3	4

[a] Vancomycin/Aztreonam, Imipenem/Cilastatin, Levofloxacin, Linezolid

[b] LFT abnormalities in tigecycline-treated patients were reported more frequently in the post therapy period than 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 pooled analysis of these trials, based on random effects model by trial weight, an adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1, 1.2) between tigecycline and comparator-treated patients (see Table 2). The cause of the imbalance has not been established. Generally, deaths were the result of worsening infection, complications of infection or underlying co-morbidities.

Table 2 Patients with outcome of death by infection type

Infection type	Tigecycline n/N	%	Comparator n/N	%	Risk Difference* % (95% CI)
cSSSI	12/834	1.4	6/813	0.7	0.7 (-0.3, 1.7)
cIAI	42/1382	3.0	31/1393	2.2	0.8 (-0.4, 2.0)
CAP	12/424	2.8	11/422	2.6	0.2 (-2.0, 2.4)
HAP	66/467	14.1	57/467	12.2	1.9 (-2.4, 6.3)
Non-VAP[a]	41/336	12.2	42/345	12.2	0.0 (-4.9, 4.9)
VAP[a]	25/131	19.1	15/122	12.3	6.8 (-2.1, 15.7)
RP	11/128	8.6	2/43	4.7	3.9 (-4.0, 11.9)
DFI	7/553	1.3	3/508	0.6	0.7 (-0.5, 1.8)
Overall adjusted	150/3788	4.0	110/3646	3.0	0.6 (0.1, 1.2) **

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections;
cSSSI = Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia;
VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infections.
Note: The studies include 300, 305, 900 (cSSSI), 301, 306, 315, 316, 400 (cIAI), 308 and 313 (CAP), 311 (HAP), 307 [Resistant gram-positive pathogen study in patients with MRSA or Vancomycin-resistant enterococcus (VRE)], and 319 (DFI with and without osteomyelitis)].

* The difference between the percentage of patients who died in tigecycline and comparator treatment groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.

** Overall adjusted (random effects model by trial weight) risk difference estimate and 95% CI.

[a] These are subgroups of the HAP population.

An analysis of mortality in all trials conducted for approved indications – cSSSI, cIAI, and CABP, including post-market trials (one in cSSSI and two in cIAI) – 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).

In comparative clinical studies, infection-related serious adverse reactions were more frequently reported for subjected treated with tigecycline (7%) versus comparator (6%). Serious adverse reactions of sepsis/septic shock were more frequently reported for subjects treated with tigecycline (2%) versus comparators (1%). Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established.

The most common adverse reactions were nausea and vomiting which generally occurred during the first 1-2 days of therapy. The majority of cases of nausea and vomiting associated with tigecycline and comparators were either mild or moderate in severity. In patients treated with tigecycline, nausea incidence was 26% (17% mild, 8% moderate, 1% severe) and vomiting incidence was 18% (11% mild, 6% moderate, 1% severe).

In patients treated for complicated skin and skin structure infections (cSSSI), nausea incidence was 35% for tigecycline and 9% for vancomycin/aztreonam; vomiting incidence was 20% for tigecycline and 4% for vancomycin/aztreonam. In patients treated for complicated intra-abdominal infections (cIAI), nausea incidence was 25% for tigecycline and 21% for imipenem/cilastatin; vomiting incidence was 20% for tigecycline and 15% for imipenem/cilastatin. In patients treated for community-acquired bacterial pneumonia (CABP), nausea incidence was 24% for tigecycline and 8% for levofloxacin; vomiting incidence was 16% for tigecycline and 6% for levofloxacin.

Discontinuation from tigecycline was most frequently associated with nausea (1%) and vomiting (1%). For comparators, discontinuation was most frequently associated with nausea (<1%).

The following adverse reactions were reported infrequently (<2%) in patients receiving tigecycline in clinical studies:

Body as a Whole: injection site inflammation, injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis

Cardiovascular System: thrombophlebitis

Digestive System: anorexia, jaundice, abnormal stools

Metabolic/Nutritional System: increased creatinine, hypocalcemia, hypoglycemia

Special Senses: taste perversion

Hemic and Lymphatic System: partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia, increased international normalized ratio (INR), thrombocytopenia

Skin and Appendages: pruritus

Urogenital System: vaginal moniliasis, vaginitis, leukorrhea

4.9 Overdose

No specific information is available on the treatment of overdosage with tigecycline. 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 hemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of action

Tigecycline 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. However, tigecycline has demonstrated bactericidal activity against isolates of *S. pneumoniae,* and *L. pneumophila.*

Resistance

To date there has been no cross-resistance observed between tigecycline and other antibacterial drugs. Tigecycline is less affected by the two major tetracycline-resistance mechanisms, ribosomal protection and efflux. Additionally, tigecycline is not affected by resistance mechanisms such as beta-lactamases (including extended spectrum beta-lactamases), target-site modifications, macrolide efflux pumps or enzyme target changes (e.g., gyrase/topoisomerases). However, some ESBL-production isolates may confer resistance to tigecycline via other resistance mechanisms. Tigecycline resistance in some bacteria (e.g., *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex) is associated with multi-drug resistant (MDR) efflux pumps.

Interaction with Other Antimicrobials

In vitro studies have not demonstrated antagonism between tigecycline and other commonly used antibacterial drugs.

Antimicrobial Activity

Tigecycline has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections.

Gram-positive bacteria

Enterococcus faecalis (vancomycin-susceptible isolates)

Staphylococcus aureus (methicillin-susceptible and -resistant isolates)

Streptococcus agalactiae

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

Streptococcus pneumoniae (penicillin-susceptible isolates)

Streptococcus pyogenes

Gram-negative bacteria

Citrobacter freundil

Enterobacter cloacae

Escherichia coli

Haemophilus influenza

Klebsiella oxytoca

Klebsiella pneumoniae

Legionella pneumophila

Anaerobic bacteria

Bacteroides fragilis

Bacteroides thetaiotaomicron

Bacteroides uniformis

Bacteroides vulgatus

Clostridium perfringens

Peptostreptococcus micros

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for tigecycline against isolates of similar genus or organism group. However, the efficacy of tigecycline in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria

Enterococcus avium

Enterococcus casseliflavus

Enterococcus faecalis (vancomycin-resistant isolates)

Enterococcus faecium (vancomycin-susceptible and -resistant isolates)

Enterococcus gallinarum

Listeria monocytogenes

Staphylococcus epidermidis (methicillin-susceptible and -resistant isolates)

Staphylococcus haemolyticus

Gram-negative bacteria

Acinetobacter baumannii[1]

Aeromonas hydrophila

Citrobacter koseri

Enterobacter aerogenes

Haemophilus influenza (ampicillin-resistant)

Haemophilus parainfluenzae

Pasteurella multocida

Serratia marcescens

Stenotrophomonas maltophilia

Anaerobic bacteria

Bacteroides distasonis

Bacteroides ovatus

Peptostreptococcus spp.

Porphyromonas spp.

Prevotella spp.

Other bacteria

Mycobacterium abscessus

Mycobacterium fortuitum

1 There have been report of the development of tigecycline resistance in Acinetobacter infections seen during the course of standard treatment. Such resistance appears to be attributable to an MDR efflux pump mechanism. While monitoring for relapse of infection is important for all infected patients, more frequent monitoring in this case is suggested. If relapse is suspected, blood and other specimens should be obtained and cultured for the presence of bacteria. All bacterial isolates should be identified and tested for susceptibility to tigecycline and other appropriate antimicrobials.

5.2 Pharmacokinetic properties

The mean pharmacokinetic parameters of tigecycline after single and multiple intravenous doses based on pooled data from clinical pharmacology studies are summarized in Table 3 Intravenous infusions of tigecycline were administered over approximately 30 to 60 minutes.

Table 3 Mean (CV%) Pharmacokinetic Parameters of Tigecycline

	Single Dose 100 mg (N=224)	Multiple Dose[c] 50 mg every 12h (N=103)
C_{max} (μg/mL)[a]	1.45 (22%)	0.87 (27%)
C_{max} (μg/mL)[b]	0.90 (30%)	0.63 (15%)
AUC (μg•h/mL)	5.19 (36%)	-
AUC_{0-24h} (μg•h/mL)	-	4.70 (36%)
C_{min} (μg/mL)	-	0.13 (59%)
$t_{½}$ (h)	27.1 (53%)	42.4 (83%)
CL (L/h)	21.8 (40%)	23.8 (33%)
CL_r (mL/min)	38.0 (82%)	51.0 (58%)
V_{ss} (L)	568 (43%)	639 (48%)

[a] 30-minute infusion

[b] 60-minute infusion

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

Distribution

The *in vitro* plasma protein binding of tigecycline ranges from approximately 71 % to 89 % at concentrations observed in clinical studies (0.1 to 1.0 μg/ml). 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 into the tissues.

Following the administration of tigecycline 100 mg followed by 50 mg every 12 hours to 33 healthy volunteers. The tigecycline $AUC_{0\text{-}12h}$ (134 μg•h/mL) in alveolar cells was approximately 78-fold higher than the $AUC_{0\text{-}12h}$ in the serum of these subjects, and the $AUC_{0\text{-}12h}$ (2.28 μg•h/mL) in epithelial lining fluid were approximately 32% higher than the $AUC_{0\text{-}12h}$ in serum, the $AUC_{0\text{-}12h}$ (1.61 μg•h/mL) of tigecycline in skin blister fluid was approximately 26% lower than the $AUC_{0\text{-}12h}$ in the serum of these subjects.

In a single-dose study, tigecycline 100 mg was administered to subjects prior to undergoing elective surgery or medical procedure for tissue extraction. Concentrations at 4 hours after tigecycline administration were in gallbladder (38-fold, n=6), lung (3.7-fold, n=5) and colon (2.3-fold, n=6) and lower in synovial fluid (0.58-fold, n=5), and bone (0.35-fold, n=6) relative to serum. The concentration of tigecycline in these tissues after multiple doses has not been studied.

Elimination

Metabolism

Tigecycline is not extensively metabolized. *In vitro* studies with tigecycline using human liver microsomes, liver slices, and hepatocytes led to the formation of only trace amounts of metabolites. In healthy male volunteers, receiving ^{14}C-tigecycline, tigecycline was the primary ^{14}C-labelled 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.

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.

Excretion

The recovery of the 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. Approximately 22% of the total dose is excreted as unchanged tigecycline in urine. Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline and its metabolites. Glucuronidation and renal excretion of unchanged tigecycline are secondary routes.

Special populations

Hepatic Impairment

In a study comparing 10 patients with mild hepatic impairment (Child Pugh A), 10 patients with moderate hepatic impairment (Child Pugh B), and 5 patients with severe hepatic impairment (Child Pugh C) to 23 age and weight matched healthy control subjects, the single-dose pharmacokinetic disposition of tigecycline was not altered in patients with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25% and the half-life of tigecycline was prolonged by 23% in patients with moderate hepatic impairment (Child Pugh B). Systemic clearance of tigecycline was reduced by 55%, and the half-life of tigecycline was prolonged by 43% patients with severe hepatic impairment (Child Pugh C). Dosage adjustment is necessary in patients with severe hepatic impairment (Child Pugh C).

Renal insufficiency

A single-dose study compared 6 subjects with severe renal impairment (creatinine clearance <30 mL/min), 4 end stage renal disease (ESRD) patients receiving tigecycline 2 hours before hemodialysis, 4 ESRD patients receiving tigecycline 1 hour after hemodialysis, and 6 healthy control subjects. The pharmacokinetic profile of tigecycline was not significantly altered in any of the renally impaired patient groups, nor was tigecycline removed by hemodialysis. No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Geriatric Patients

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

Pediatric Patients

A single-dose safety, tolerability, and pharmacokinetic study of tigecycline patients aged 8-16 years who recently recovered from infections was conducted. The doses administered were 0.5, 1, or 2 mg/kg. The study showed that for children aged 12-16 years (n=16) a dosage of 50 mg twice daily would likely result in exposures comparable to those observed in adults with the approved dosing regimen. Large variability observed in children aged 8 to 11 years of age (n=8) required additional study to determine the appropriate dosage.

A subsequent tigecycline dose-finding study was conducted in 8-11 year old patients with cIAI, cSSSI, or CABP. The doses of tigecycline studied were 0.75 mg/kg (n=17), 1 mg/kg (n=21), and 1.25 mg/kg (n=20). This

study showed that for children aged 8-11 years, a 1.2 mg/kg dose would likely result in exposures comparable to those observed in adults resulting with the approved dosing regimen.

Gender

In a pooled analysis of 38 women and 298 men participating in clinical pharmacology studies, there was no significant difference in the mean (±SD) tigecycline clearance between women (20.7±6.5 L/h) and men (22.8±8.7 L/h). Therefore, no dosage adjustment is necessary based on gender.

Race

In a pooled analysis of 73 Asian subjects, 53 Black subjects, 15 Hispanic subjects, 190 White subjects, and 3 subjects classified as "other" participating in clinical pharmacology studies, there was no significant difference in the mean (±SD) tigecycline clearance among the Asian subjects (28.8±8.8 L/h). Black subjects (23.0±7.8 L/h), Hispanic subjects (24.3±6.5 L/h), White subjects (22.1±8.9 L/h). Therefore, no dosage adjustment is necessary based on race.

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 discoloring 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) 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.

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

6.2 Incompatibilities

The following active substances should not be administered simultaneously through the same Y-site as tigecycline: Amphotericin B, amphotericin B lipid complex, diazepam, esomeprazole and omeprazole.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Clear glass vial Type I with grey chlorobutyl rubber stoppers, sealed with aluminium/polypropylene flip-off caps with or without a paper box of 1, 5, 10, 20, 25, 50 and 100 vials.

6.6 Special precautions for disposal and other handling

The powder should be reconstituted with 5.3 mL of 0.9% sodium chloride solution for injection, 5% dextrose 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 withdrawn from the vial and added to a 100 ml intravenous container for infusion or other suitable infusion container.

For a 100 mg dose, reconstitute using two vials into a 100 ml intravenous container or other suitable infusion container. 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 discoloration (e.g., green or black) prior to administration.

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

Compatible intravenous solutions include: 0.9% sodium chloride solution for injection, 5% dextrose solution for injection, and Lactated Ringer's solution for injection.

When administered through a Y-site, compatibility of tigecycline diluted in 0.9% sodium chloride solution 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 authorization holder

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8. Marketing authorization number(s)

1A 15046/65 (NG)

9. Date of first authorization/renewal of the authorization

31 May, 2022

10. Date of revision of the text

6 June, 2023