For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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Tigecycline for Injection USP 50 mg (Lyophilized)

TIGIVERI® 50 mg

Composition :

Each vial contains :

Tigecycline USP 50 mg

DOSAGE FORM

Lyophilized powder for reconstitution and I.V. use only

PHARMACOLOGY

Pharmacokinetics

Absorption

In clinical studies using the therapeutic dosage regimen of 100 mg loading dose followed by a maintenance dose of 50 mg every 12h, C_{max} was 0.87 mcg/mL for 30-minute infusions and 0.63 mcg/mL for 60-minute infusions. The $AUC_{0\text{-}24h}$ value was 4.70 mcg.h/mL.

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). 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 mcg.h/mL) in the alveolar cells was approximately 78-fold higher than the $AUC_{0\text{-}12h}$ in the serum, and the $AUC_{0\text{-}12h}$ (2.28 mcg.h/mL) in epithelial lining fluid was approximately 32% higher than the $AUC_{0\text{-}12h}$ in serum. The $AUC_{0\text{-}12h}$ (1.61 mcg.h/mL) of tigecycline in skin blister fluid was approximately 26% lower than the $AUC_{0\text{-}12h}$ in the serum of 10 healthy subjects. In a single-dose study, after administration of 100 mg tigecycline to subjects prior to undergoing elective surgery or medical procedure for tissue extraction, concentra-tions at 4 hours were higher in the gallbladder (38-fold, n=6), lungs (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.

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 the urine and faeces, but a glucuronide, an N-acetyl metabolite and a tigecycline epimer (each at no more than 10% of the administered dose) were also present.

Elimination

The recovery of total radioactivity in the faeces and urine following administration of ^{14}C-tigecycline indicates that 59% of the dose is eliminated by biliary/faecal excretion, and 33% is excreted in urine. 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. The total clearance of tigecycline is approximately 24 L/hr following I.V. infusion. Tigecycline shows a mean terminal elimination half-life of 42 hours following multiple doses of 50 mg every 12 hours (initial dose of 100 mg).

Pharmacodynamics

Mechanism of Action

Tigecycline, a glycylcycline, 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 ribosomes. 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. In general, tigecycline is considered bacteriostatic; however, tigecycline has demonstrated bactericidal activity against isolates of Streptococcus pneumoniae and Legionella pneumophila.

Mechanism(s) of Resistance

Tigecycline demonstrates time-dependent activity *in vitro*.

To date, there has been no cross-resistance observed between tigecycline and other antibacterials. Tigecycline is not 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). Tigecycline resistance in some bacteria (e.g., Acinetobacter calcoaceticus-Acinetobacter baumannii complex) is associated with multi-drug resistant (MDR) efflux pumps.

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

Facultative Gram-positive bacteria

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 pneumoniae (penicillin-susceptible isolates)

Streptococcus pyogenes

Viridans group streptococci

Facultative Gram-negative bacteria

Citrobacter freundii

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae (beta-lactamase negative isolates)

Klebsiella oxytoca

Klebsiella pneumoniae

Legionella pneumophila

Anaerobic bacteria

Bacteroides fragilis

Bacteroides thetaiotaomicron

Bacteroides uniformis

Bacteroides vulgatus

Clostridium perfringens

Peptostreptococcus micros

At least 90% of the following bacteria exhibit in vitro minimum inhibitory concentrations (MICs) that are at concentrations that are achievable using the prescribed dosing regimens. However, the clinical significance of this is unknown because the safety and effectiveness of tigecycline in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Facultative Gram-posItlve 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

Facultative Gram-negative bacteria

*Acinetobacter baumannii**

Aeromonas hydrophila

Citrobacter koseri

Enterobacter aerogenes

Haemophilus influenzae (ampicillin-resistant)

Haemophilus parainfluenzae

Pasteurella multocida

Serratia marcescens

Stenotrophomonas maltophilia

Anaerobic bacteria

Bacteroides distasonis

Bacteroides ovatus

Peptostretococcus spp.

Porphyromonas spp.

Prevotella spp.

Other bacteria

Mycobacterium abscessus

Mycobacterium fortuitum

*There have been reports 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.

Inherently resistant organisms

Pseudomonas aeruginosa

Other species for which acquired resistance may be a problem include *Burkholderia cepacia, Morganella morganii, Proteus spp.* and *Providencia spp.*

INDICATIONS

Tigecycline is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the conditions listed below for patients who are 18 years of age and older:

- **Complicated Intra-Abdominal Infections**

  Complicated intra-abdominal infections caused by *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.*

- **Complicated Skin and Skin Structure Infections**

  Complicated skin and skin structure infections caused by *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.*

- **Community-Acquired Bacterial Pneumonia**

  Community-acquired bacterial pneumonia caused by *Streptococcus pneumoniae (penicillin-susceptible isolates), including cases with concurrent bacteremia, Haemophilus influenzae (beta-lactamase-negative isolates), and Legionella pneumophila.*

DOSAGE AND ADMINISTRATION

Adults

The recommended dosage regimen for Tigecycline is an initial dose of 100 mg, followed by 50 mg every 12 hours. I V. 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.

Renal Impairment

The pharmacokinetic profile of tigecycline was not significantly altered in any of the renally impaired patient groups, nor was tigecycline removed by haemodialysis. No dosage adjustment of Tigecycline is necessary in patients with renal impairment or in patients undergoing haemodialysis.

Hepatic Impairment

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 tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response.

Method of Administration

Each vial of Tigecycline should be reconstituted with 5 mL of 0.9% Sodium Chloride solution for 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 add to a 100 mL I.V. bag for infusion (for a 100 mg dose, reconstitute two vials; for a 50 mg dose, reconstitute one vial). The maximum concentration in the I.V. bag should be 1 mg/mL. Parenteral drug products should be inspected visually for particulate matter and discolouration (e.g., green or black) prior to administration.

Tigecycline may be administered intravenously through a dedicated I.V. line or through a Y-site. If the same I.V. line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of Tigecycline with 0 9%. Sodium Chloride solution for Injection, 5% Dextrose solution for Injection or Lactated Ringer's solution for Injection. The injection should be made with an infusion solution compatible with tigecycline and with any other drug(s) administered via this common line.

Storage : Store at controlled room temperature (below 25°C).

Mfd. at :

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(A WHO-GMP Certified)

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