Biocon

℞

Tigecycline for Injection

TIGOVAR™ ËOaÉÉUÉU

COMPOSITION

Each vial contains:

Tigecycline	50 mg

PHARMACEUTICAL FORM

50 mg lyophilized powder for reconstitution in a single-dose vial.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Antibacterials for systemic use

ATC code: J01AA12

Tigecycline is a tetracycline derivative (a glycylcycline) for intravenous infusion. The chemical name of Tigecycline is (4S,4aS,5aR,12aS)-9-[2-(tert-butylamino)acetamido]-4,7bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide. The empirical formula is $C_{29}H_{39}N_5O_8$ and the molecular weight is 585.65

Mechanism of Action

Tigecycline, a glycylcycline, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking the 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.

Pharmacokinetic Properties

Absorption/Distribution

The plasma protein binding of Tigecycline ranges from approximately 71% to 89% at concentrations (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 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 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, and the $AUC_{0\text{-}12h}$ (2.28 µg·h/mL). In epithelial lining fluid was approximately 32% higher than the $AUC_{0\text{-}12h}$ in serum. The $AUC_{0\text{-}12h}$ (1.61 µg·h/mL) of Tigecycline in skin blister fluid was approximately 28% lower than the $AUC_{0\text{-}12h}$ in the serum.

Metabolism/Excretion

Tigecycline is not extensively metabolized. Unchanged drug excretes 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. Of the total dose administered, 59% is eliminated by biliary/fecal excretion and 33% by 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.

Preclinical Safety Data

In 2 week studies, decreased erythrocytes, reticulocytes, leukocytes, and platelets, in association with bone marrow hypocellularity, have been seen with Tigecycline at exposures of 8 and 10 times the human daily dose based on AUC in rats and dogs, (AUC of approximately 50 and 60 µg·hr/mL at doses of 30 and 12 mg/kg/day), respectively. These alterations were shown to be reversible after 2 weeks of dosing.

Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of Tigecycline. No mutagenic or clastogenic potential was found in a battery of tests, including *in vitro* chromosome aberration assay in Chinese hamster ovary (CHO) cells, *in vitro* forward mutation assay in CHO cells (HGRPT locus), *in vitro* forward mutation assays in mouse lymphoma cells, and *in vivo* mouse micronucleus assay. Tigecycline did not affect mating or fertility in rats at exposures up to 5 times the human daily dose based on AUC (28 µg·hr/mL at 12 mg/kg/day). In female rats, there were no compound-related effects on ovaries or estrous cycles at exposures up to 5 times the human daily dose based on AUC.

CLINICAL PARTICULARS

Therapeutic Indications

Tigecycline is a tetracycline-class antibacterial indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the conditions listed below for patients 18 years of age and older:

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* group (includes *S anginosus*, *S intermedius*, and *S constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*.

Complicated Intra-abdominal Infections

Complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *E. coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* group (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

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

Posology and Method of Administration

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.

Patients With 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.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Because of effects on tooth development, use in patients under 8 years of age is not recommended.

Geriatric Use

No significant difference in Tigecycline exposure was observed between healthy elderly subjects and younger subjects following a single 100 mg dose of Tigecycline.

Preparation and Handling

Each vial of Tigecycline 50 mg should be reconstituted with 5.3 mL of 0.9% Sodium Chloride Injection IP, 5% Dextrose Injection IP, or lactated Ringer's injection USP 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 intravenous bag for infusion (for a 100 mg dose, reconstitute 2 vials; for a 50 mg dose, reconstitute 1 vial). The maximum concentration in the intravenous bag 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 (eg, green or black) prior to administration. Once reconstituted, Tigecycline 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 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP may be stored refrigerated at 2°C to 8°C (36°F to 46°F) for up to 48 hours following immediate transfer of the reconstituted solution into the intravenous bag.

Tigecycline 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 Tigecycline 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.

Compatibilities

Compatible intravenous solutions 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.

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.

Contraindications

Tigecycline is contraindicated for use in patients who have known hypersensitivity to Tigecycline.

Special Warnings and Precautions for Use

Anaphylaxis/anaphylactoid Reactions

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

Hepatic 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.

Mortality Imbalance and Lower Cure Rates in Ventilator-Associated Pneumonia

A trial of patients with hospital-acquired pneumonia failed to demonstrate the efficacy of Tigecycline and had lower cure rates. In this trial, greater mortality was seen in patients with ventilator-associated pneumonia who received Tigecycline when compared with comparator-treated patients.

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

Biocon

℞

Tigecycline for Injection

TIGOVAR™

ËOaÉÉUÉU

abnormalities suggestive of acute 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.

Use During Pregnancy
Tigecycline may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking Tigecycline, the patient should be apprised of the potential hazard to the fetus.

Tooth Development
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).

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.

Patients With Intestinal Perforation
Caution should be exercised when considering Tigecycline monotherapy in patients with complicated intra-abdominal infections (cIAI), as studies indicate intestinal perforations had developed.

Tetracycline-class Effects
Tigecycline is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased blood urea nitrogen [BUN], azotemia, acidosis, arid hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of Tigecycline.

Superinfection
As with other antibacterial drugs, use of Tigecycline may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfections occur, appropriate measures should be taken.

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.

Drug Interactions
Warfarin
Prothrombin time or other suitable anticoagulation test should be monitored if Tigecycline is administered with warfarin.

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

Pregnancy and Lactation
Pregnancy: Category D
Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, ^{14}C-labeled Tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of Tigecycline was associated with slight reductions in fetal weights and an increased incidence of minor skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively (28 µg·hr/mL and 6 µg·hr/mL at 12 and 4 mg/kg/day). An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.

There are no adequate and well-controlled studies of Tigecycline in pregnant women. TIGOVAR™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
Results from animal studies using ^{14}C-labeled 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 nursing pups as a result of exposure via maternal milk.

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 TIGOVAR™ is administered to a nursing woman.

Effects on Ability to Drive and Use Machines
No studies on the effects of Tigecycline on the ability to drive and use machines have been performed. Dizziness may occur and this may have an effect on driving and use of machines.

Undesirable Effects
In clinical trials, patients treated with Tigecycline were discontinued due to adverse reactions in 7% of patients compared to 6% for all comparators. The table below shows the summary of treatment-emergent adverse reactions.

Body System	Adverse Reactions
Body as a Whole	Abdominal pain, abscess, asthenia, headache, infection, injection site inflammation, injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis
Cardiovascular System	Phlebitis, thrombophlebitis
Digestive System	diarrhea, dyspepsia, nausea, vomitting, anorexia, jaundice, abnormal stools
Hemic and Lymphatic System	Anemia, partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia, increased international normalized ratio (INR), thrombocytopenia
Metabolic and Nutritional	Increased alkaline phosphatase, increased amylase,
Nervous System	bilirubinemia, increased BUN*, healing abnormal, hypoproteinemia, increased SGOT*, increased SGPT*, increased creatinine, hypocalcemia, hypoglycemia, hyponatremia Dizziness
Special Senses	Taste perversion
Skin and Appendages	Rash
Urogenital System	Vaginal moniliasis, vaginitis, leukorrhea

**Note: SGOT: serum glutamate oxaloacetate transaminase*
SGPT: serum glutamate pyruvate transaminase
BUN: blood urea nitrogen.

In the trials conducted, which included a comparator, death occurred in 4.0% of patients receiving Tigecycline and 3.0% of patients receiving comparator drugs. In a pooled analysis of these trials, based on a random effects model by trial weight, an adjusted risk difference of all-cause mortality was 0.6% between Tigecycline and comparator-treated patient; the cause of the imbalance was not established. Generally, deaths were the result of worsening infection, complications of infection or underlying co-morbidities.

Post-Marketing Experience
The following adverse reactions have been identified during post-approval use of Tigecycline. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure.

- anaphylaxis/anaphylactoid reactions
- acute pancreatitis
- hepatic cholestasis, and jaundice

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 reported an increased incidence of nausea and vomiting. In single-dose intravenous toxicity studies conducted with Tigecycline in mice, the estimated median lethal dose (LD_{50}) was 124 mg/kg in males and 98 mg/kg in females. In rats, the estimated LD_{50} was 106 mg/kg for both sexes. Tigecycline is not removed in significant quantities by hemodialysis.

PHARMACEUTICAL PARTICULARS

Shelf Life
24 months

Storage and Precautions
Store below 25°C.
Keep out of reach of children.

Special Precautions for Disposal and Other Handling
No special requirements.

Pack Size
5mL flint tubular vails

Nature and Contents of Container
Tigecycline for Injection is available in a vial containing Tigecycline 50 mg.

For further details, please contact:
Medical Advisor
Biocon Limited
20th KM, Hosur Road
Electronics City
Bangalore – 560100, India.

TM - Trade Mark of Biocon Limited

To report adverse events and/or product complaints visit our website www.biocon.com or call toll free number: 1800 102 9465 or e-mail us at drugsafety@biocon.com.

BF/LL/0178/01