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

Tigecycline For Injection IP 50 mg

(Lyophilized)

TIGEVAR®

Each vial contains:

Tigecycline IP	50 mg
Excipients	q.s.

DESCRIPTION:

Tigecycline is tetracycline derivative. The chemical name of Tigecycline is 2-Naphthacenecarboxamide,4,7-bis(dimethylamino)-9-[[[(1,1-dimethylethyl)amino]acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-(4S,4aS,5aR,12aS).

The empirical formula is $C_{29}H_{39}N_5O_8$ and the molecular weight is 585.7 g/mol.

THERAPEUTIC INDICATIONS:

Tigecycline For Injection is indicated in adults and in children from the age of eight years for the treatment of the following infections (infections cause by susceptible isolates of the designated microorganism)

- Complicated skin and soft tissue infections (cSSTI), excluding diabetic foot infections.
- Complicated Intra-Abdominal Infections (cIAI).
- Community-Acquired Bacterial Pneumonia.

Tigecycline For Injection should be used only in situations where other alternative antibiotics are not suitable.

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

POSOLOGY AND METHOD OF ADMINISTRATION:

Adults

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

Children and adolescents (8 to <17 years of age)

Children aged 8 to <12 years: 1.2 mg/kg of tigecycline every 12 hours intravenously to a maximum dose of 50 mg every 12 hours for 5 to 14 days.

Adolescents aged 12 to <18 years: 50 mg of tigecycline every 12 hours for 5 to 14 days.

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

The recommended duration of treatment with tigecycline for Complicated skin and soft tissue infections (cSSTI), excluding diabetic foot infections & Complicated Intra-Abdominal Infections (cIAI) is 5-14 days and for Community-Acquired Bacterial Pneumonia is 7-14 days.

Elderly

No dosage adjustment is necessary in elderly patients.

Hepatic impairment

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

In patients (including paediatrics) with severe hepatic impairment (Child Pugh C), the dose of tigecycline should be reduced by 50%. Adult dose should be reduced to 25 mg every 12 hours following the 100 mg loading dose. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response.

Renal impairment

No dosage adjustment is necessary in patients with renal impairment or in patients undergoing haemodialysis.

Paediatric population

The safety and efficacy of tigecycline in children under 8 years of age have not been established. No data are available.

Tigecycline should not be used in children aged under 8 years because of teeth discolouration.

Method of administration:

Tigecycline is administered only by intravenous infusion over 30 to 60 minutes. Tigecycline should be preferably administered over a 60-minute length of infusion in paediatric patients.

Instructions on reconstitution:

Each vial of tigecycline should be reconstituted with 5.2 ml of 0.9% w/v sodium chloride injection or 5% w/v dextrose injection to achieve a concentration of 10 mg/ml of tigecycline.

Withdraw 5 ml of the reconstituted solution from the vial and add to a 100 ml intravenous infusion bag for infusion (for a 100 mg dose, reconstitute two vials; for a 50 mg dose, reconstitute one vial).

The maximum concentration in the bag should be 1mg/ml.

Once reconstitution, Tigecycline may be stored at room temperature for up to 24 hours.

Alternatively, Tigecycline may be stored refrigerated at 2 to 8℃ for up to 45 hours following immediate transfer of the reconstituted solution into the intravenous bag.

CONTRAINDICATIONS:

Hypersensitivity to the active substance.

Patients hypersensitive to tetracycline class antibiotics may be hypersensitive to tigecycline.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

In complicated skin and soft tissue infections (cSSTI), complicated intra-abdominal infections (cIAI), diabetic foot infections, nosocomial pneumonia and studies in resistant pathogens, a numerically higher mortality rate among tigecycline treated patients has been observed as compared to the comparator treatment. The causes of these findings remain unknown, but poorer efficacy and safety than the study comparators cannot be ruled out.

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 cSSTI or cIAI is identified after initiation of tigecycline therapy consideration should be given to instituting alternative antibacterial therapy that has been demonstrated to be efficacious in the treatment of the specific type of infection(s) present.

Anaphylaxis

Anaphylaxis/anaphylactoid reactions, potentially life-threatening, have been reported with tigecycline.

Hepatic failure

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

Tetracycline class antibiotics

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. Tigecycline may have adverse reactions similar to tetracycline class antibiotics. Such reactions may include photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic action which has led to increased BUN, azotaemia, acidosis, and hyperphosphataemia.

Pancreatitis

Acute pancreatitis, which can be serious, has occurred (frequency: uncommon) 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. 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.

Coagulopathy

Tigecycline may prolong both prothrombin time (PT) and activated partial thromboplastin time (aPTT). Additionally, hypofibrinogenaemia has been reported with the use of tigecycline. Therefore, blood coagulation parameters such as PT or other suitable anticoagulation test, including blood fibrinogen, should be monitored prior to treatment initiation with tigecycline and regularly while on treatment. Special care is recommended in seriously ill patients and in patients also using anticoagulants.

Underlying diseases

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

Limited experience is also available in treating patients with concurrent bacteraemia (5.6 %). Therefore, caution is advised when treating such patients.

Consideration should be given to the use of combination antibacterial therapy whenever tigecycline is to be administered to severely ill patients with cIAI secondary to clinically apparent intestinal perforation or patients with incipient sepsis or septic shock.

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.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibacterial agent.

The use of tigecycline may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy.

Paediatric population

The use of tigecycline for the treatment of infections in paediatric patients aged 8 years and older is very limited. Consequently, use in children should be restricted to those clinical situations where no alternative antibacterial therapy is available.

Abdominal pain is commonly reported in children as it is in adults. Abdominal pain may be indicative of pancreatitis. If pancreatitis develops, treatment with tigecycline should be discontinued.
Liver function tests, coagulation parameters, haematology parameters, amylase and lipase should be monitored prior to treatment initiation with tigecycline and regularly while on treatment.
Tigecycline Injection should not be used in children under 8 years of age due to the lack of safety and efficacy data in this age group and because tigecycline may be associated with permanent teeth discolouration.

DRUG INTERACTION WITH OTHER MEDICINAL PRODUCTS:
Tigecycline may prolong both prothrombin time (PT) and activated partial thromboplastin time (aPTT), the relevant coagulation tests should be closely monitored when tigecycline is co-administered with anticoagulants. Warfarin did not affect the pharmacokinetic profile of tigecycline.
Tigecycline is not extensively metabolised. Therefore, clearance of tigecycline is not expected to be affected by active substances that inhibit or induce the activity of the CYP450 isoforms. In vitro, tigecycline is neither a competitive inhibitor nor an irreversible inhibitor of CYP450 enzymes.
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.
Concurrent use of antibiotics with oral contraceptives may render oral contraceptives less effective.
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.
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.

PREGNANCY, LACTATION AND FERTILITY
Pregnancy: Tigecycline should not be used during pregnancy unless the clinical condition of the woman requires treatment with tigecycline.
Lactation: It is unknown whether tigecycline/metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from tigecycline therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Fertility: The effects of tigecycline on fertility in humans have not been studied.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Dizziness may occur and this may have an effect on driving and use of machines.

UNDESIRABLE EFFECTS
Infections and infestations: sepsis/septic shock, pneumonia, abscess, infections.
Blood and lymphatic system disorders: prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time, thrombocytopenia, increased international normalized ratio (INR) (PT), hypofibrinogenaemia.
Immune system disorders: anaphylaxis/ anaphylactoid reactions*.
Metabolism and nutrition disorders: hypoglycaemia, hypoproteinaemia
Nervous system disorders: dizziness
Vascular disorders: phlebitis, thrombophlebitis
Gastrointestinal disorders: nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, anorexia, acute pancreatitis.
Hepatobiliary disorders: elevated aspartate aminotransferase (AST) in serum, and elevated alanine aminotransferase (ALT) in serum, hyperbilirubinaemia, jaundice, liver injury, mostly cholestatic, hepatic failure*.
Skin and subcutaneous tissue disorders: pruritus, rash, severe skin reactions, including Stevens-Johnson Syndrome*.
General disorders and administration site conditions: impaired healing, injection site reaction, headache, injection site inflammation, injection site pain, injection site oedema, injection site phlebitis.
Investigations: elevated amylase in serum, increased blood urea nitrogen (BUN).

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

PHARMACOLOGICAL PROPERTIES:
Pharmacotherapeutic Group: Antibacterials for systemic use, tetracyclines
ATC code: J01AA12
Pharmacodynamics properties:
Tigecycline, a glycylcycline antibiotic, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains.
In general, tigecycline is considered bacteriostatic. At 4 times the minimum inhibitory concentration (MIC), a 2-log reduction in colony counts was observed with tigecycline against Enterococcus spp., Staphylococcus aureus, and Escherichia coli.

PHARMACOKINETIC PROPERTIES:
Absorption: Tigecycline is administered intravenously and therefore has 100 % bioavailability.
Distribution: The in vitro plasma protein binding of tigecycline ranges from approximately 71 % to 89 % at concentrations 0.1 to 1.0 mcg/ml.
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.
Biotransformation: On average, it is estimated that less than 20 % of tigecycline is metabolised before excretion. In healthy male volunteers, following the administration of 14C-tigecycline, unchanged tigecycline was the primary 14C-labelled material recovered in urine and faeces, but a glucuronide, an N-acetyl metabolite and a tigecycline epimer were also present.
Elimination: The recovery of the total radioactivity in faeces and urine following administration of 14C-tigecycline indicates that 59 % of the dose is eliminated by biliary/faecal excretion, and 33 % is excreted in urine.
Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline. Glucuronidation and renal excretion of unchanged tigecycline are secondary routes.
The total clearance of tigecycline is 24 L/h after intravenous infusion. Renal clearance is approximately 13 % of total clearance. Tigecycline shows a polyexponential elimination from serum with a mean terminal elimination half-life after multiple doses of 42 hours although high interindividual variability exists.
Special Population
Hepatic impairment: The single-dose pharmacokinetic disposition of tigecycline was not altered in patients with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25 % and 55 % and the half-life of tigecycline was prolonged by 23 % and 43 % in patients with moderate or severe hepatic impairment (Child Pugh B and C).
Renal impairment: The single dose pharmacokinetic disposition of tigecycline was not altered in patients with renal insufficiency (creatinine clearance <30 ml/min, n=6).

Storage:
Store protected from light and moisture at a temperature not exceeding 30ºC.
Storage after reconstitution: Once reconstitution, Tigecycline may be stored at room temperature for up to 24 hours.
Alternatively, Tigecycline may be stored refrigerated at 2 to 8ºC for up to 45 hours following immediate transfer of the reconstituted solution into the intravenous bag.

Presentation:
Primary Packing: 5 ml clear glass tubular vial USP Type-I.
Secondary Packing: Each vial placed in HIPS white tray, packed in printed monocarton along with package insert.

Mfd. By: **Bharat Parenterals Limited**
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