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

TICPLAT 200

Lyophilized Powder
For I.M./I.V. use only

℞

Teicoplanin 200 mg powder for solution for injection or infusion

Qualitative and quantitative composition
Each vial contains 200 mg Teicoplanin equivalent to 200,000 IU

Pharmaceutical form:
White or almost white lyophilized powder or cake free of foreign particles.

After reconstitution: Clear, colourless to light yellow solution.

Appearance of diluted solution before infusion with compatible diluents: Clear, colourless to light yellow solution.

Clinical Particulars
Therapeutic Indications:

TICPLAT 200 is indicated in adults and in children from birth for the parenteral treatment of the following infections:
- complicated skin and soft tissue infections,
- bone and joint infections,
- hospital acquired pneumonia,
- community acquired pneumonia,
- complicated urinary tract infections,
- infective endocarditis,
- peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD),
- bacteraemia that occurs in association with any of the indications listed above.

Where appropriate, teicoplanin should be administered in combination with other antibacterial agents.

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

Posology and method of administration:

Posology

The dose and duration of treatment should be adjusted according to the underlying type and severity of infection and clinical response of the patient, and patient factors such as age and renal function.

Measurement of serum concentrations

Teicoplanin trough serum concentrations should be monitored at steady state after completion of the loading dose regimen in order to ensure that a minimum trough serum concentration has been reached:

- For most Gram-positive infections, teicoplanin trough levels of at least 10 mg/L when measured by High Performance Liquid Chromatography (HPLC), or at least 15 mg/L when measured by Fluorescence Polarization Immunoassay (FPIA) method.
- For endocarditis and other severe infections, teicoplanin trough levels of 15-30 mg/L when measured by HPLC, or 30-40 mg/L when measured by FPIA method.

During maintenance treatment, teicoplanin trough serum concentrations monitoring may be performed at least once a week to ensure that these concentrations are stable.

Adults and elderly patients with normal renal function

Indications	**Loading dose**		**Maintenance dose**	
	Loading dose regimen	**Targeted trough concentrations at day 3 to 5**	**Maintenance dose**	**Targeted trough concentrations during maintenance**
• Complicated skin and soft tissue infections. • Pneumonia. • Complicated urinary tract infections	6 mg/kg body weight every 12 hours for 3 intravenous or intramuscular administrations	>15 mg/L[1]	6 mg/kg body weight intravenous or intramuscular once a day	>15 mg/L[1] once a week
• Bone and joint infections	12 mg/kg body weight every 12 hours for 3 to 5 intravenous administrations	>20 mg/L[1]	12 mg/kg body weight intravenous or intramuscular once a day	>20 mg/L[1]
• Infective endocarditis	12 mg/kg body weight every 12 hours for 3 to 5 intravenous administrations	30-40 mg/L[1]	12 mg/kg body weight intravenous or intramuscular once a day	>30 mg/L[1]

[1] Measured by FPIA

The dose is to be adjusted on bodyweight whatever the weight of the patient.

Duration of treatment

The duration of treatment should be decided based on the clinical response. For infective endocarditis a minimum of 21 days is usually considered appropriate. Treatment should not exceed 4 months.

Combination therapy

Teicoplanin has a limited spectrum of antibacterial activity (Gram positive). It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a high suspicion that the most likely pathogen(s) would be suitable for treatment with teicoplanin.

Elderly population

No dose adjustment is required, unless there is renal impairment.

Adults and elderly patients with impaired renal function

Dose adjustment is not required until the fourth day of treatment, at which time dosing should be adjusted to maintain a serum trough concentration of at least 10 mg/L when measured by HPLC, or at least 15 mg/L when measured by FPIA method.

After the fourth day of treatment:

- In mild and moderate renal insufficiency (creatinine clearance 30-80 mL/min): maintenance dose should be halved, either by administering the dose every two days or by administering half of this dose once a day.
- In severe renal insufficiency (creatinine clearance less than 30 mL/min) and in haemodialysed patients: dose should be one-third of the usual dose, either by administering the initial unit dose every third day or by administering one-third of this dose once a day.

Teicoplanin is not removed by dialysis.

Patients in continuous ambulatory peritoneal dialysis (CAPD)

After a single intravenous loading dose of 6 mg/kg bodyweight, 20 mg/L is administered in the bag of the dialysis solution in the first week, 20 mg/L in different bags the second week and then 20 mg/L in the overnight bag in the third week.

Paediatric population

The dose recommendations are the same in adults and children above 12 years of age.

Neonates and infants up to the age of 2 months:

Loading dose
One single dose of 16 mg/kg body weight, administered intravenously by infusion on the first day.

Maintenance dose
One single dose of 8 mg/kg body weight administered intravenously by infusion once a day.

Children (2 months to 12 years):

Loading dose
One single dose of 10 mg/kg body weight administered intravenously every 12 hours, repeated 3 times.

Maintenance dose
One single dose of 6-10 mg/kg body weight administered intravenously once a day.

Method of administration

Teicoplanin should be administered by the intravenous or intramuscular route. The intravenous injection may be administered either as a bolus over 3 to 5 minutes or as a 30-minute infusion.

Only the infusion method should be used in neonates.

For instructions on reconstitution and dilution of the medicinal product before administration,

Pharmacokinetics Properties

Absorption

Teicoplanin is administered by parenteral route (intravenously or intramuscularly). After intramuscular administration, the bioavailability of teicoplanin (as compared to intravenous administration) is almost complete (90%). After six daily intramuscular administrations of 200 mg the mean (SD) maximum teicoplanin concentration (C_{max}) amounts to 12.1 (0.9) mg/L and occurs at 2 hours after administration.

After a loading dose of 6 mg/kg administered intravenously every 12 hours for 3 to 5 administrations, C_{max} values range from 60 to 70 mg/L and C_{trough} are usually above 10 mg/L. After an intravenous loading dose of 12 mg/kg administered every 12 hours for 3 administrations, mean values of C_{max} and C_{trough} are estimated to be around 100 mg/L and 20 mg/L, respectively.

After a maintenance dose of 6 mg/kg administered once daily C_{max} and C_{trough} values are approximately 70 mg/L and 15 mg/L, respectively. After a maintenance dose of 12 mg/kg once daily C_{trough} values range from 18 to 30 mg/L.

When administered by oral route teicoplanin is not absorbed from the gastrointestinal tract. When administered by oral route at 250 or 500 mg single dose to healthy subjects, teicoplanin is not detected in serum or urine but only recovered in feces (about 45% of the administered dose) as unchanged medicinal product.

Distribution

The binding to human serum proteins ranges from 87.6 to 90.8% without any variation in function of the teicoplanin concentrations. Teicoplanin is mainly bound to human serum albumin. Teicoplanin is not distributed in red cells.

The volume of distribution at steady-state (Vss) varies from 0.7 to 1.4 L/kg. The highest values of Vss are observed in the recent studies where the sampling period was superior to 8 days.

Teicoplanin distributed mainly in lung, myocardium and bone tissues with tissue/serum ratios superior to 1. In blister fluids, synovial fluid and peritoneal fluid the tissue/serum ratios ranged from 0.5 to 1. Elimination of teicoplanin from peritoneal fluid occurs at the same rate as from serum. In pleural fluid and subcutaneous fat tissue the tissue/serum ratios are comprised between 0.2 and 0.5. Teicoplanin does not readily penetrate into the cerebrospinal fluid (CSF).

Biotransformation

Unchanged form of teicoplanin is the main compound identified in plasma and urine, indicating minimal metabolism. Two metabolites are formed probably by hydroxylation and represents 2 to 3% of the administered dose.

Elimination

Unchanged teicoplanin is mainly excreted by urinary route (80% within 16 days) while 2.7% of the administered dose is recovered in feces (via bile excretion) within 8 days following administration.

Elimination half-life of teicoplanin varies from 100 to 170 hours in the most recent studies where blood sampling duration is about 8 to 35 days.

Teicoplanin has a low total clearance in the range of 10 to 14 mL/h/kg and a renal clearance in the range of 8 to 12 mL/h/kg indicating that teicoplanin is mainly excreted by renal mechanisms.

Linearity

Teicoplanin exhibited linear pharmacokinetics at dose range of 2 to 25 mg/kg.

Special populations

- *Renal impairment:*

As teicoplanin is eliminated by renal route, teicoplanin elimination decreases according to the degree of renal impairment. The total and renal clearances of teicoplanin depends on the creatinine clearance.

- *Elderly patients:*

In the elderly population the teicoplanin pharmacokinetics is not modified unless in case of renal impairment.

- *Paediatric population*

A higher total clearance (15.8 mL/h/kg for neonates, 14.8 mL/h/kg for a mean age 8 years) and a shorter elimination half-life (40 hours neonates; 58 hours for 8 years) are observed compared to adult patients.

Pharmaceutical Particulars:

List of Excipients:

Sodium Chloride

Incompatibilities:

Teicoplanin and aminoglycoside are incompatible when mixed directly and must not be mixed before injection.

If teicoplanin is administered in combination therapy with other antibiotics, the preparation must be administered separately.

This medicinal product must not be mixed with other medicinal products except those mentioned in section *Special precautions for disposal and other handling.*

Special precaution for storage:

Unopened vials: Store below 30°C. Keep out of reach of children.
Reconstituted solution with water for injection:

Chemical and physical in-use stability of the reconstituted solution prepared as recommended has been demonstrated for 24 hours at 2 to 8°C.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

After further dilution:

Chemical and physical in-use stability of the reconstituted solution prepared as recommended has been demonstrated for 24 hours at 2 to 8°C.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Nature and content of container:

10 ml clear tubular vial containing Teicoplanin 200 mg

Special Precaution for disposal and other handling

This medicinal product is for single use only

Preparation of reconstituted solution:

The solution is reconstituted by adding 3.14 mL of water for injection to the 200 mg powder vial. The water is slowly added to the vial which should be rotated until all the powder is dissolved to avoid foaming. If foam is developed, allow the solution to stand for approximately 15 minutes so that the foam disappears. Only clear, colourless to light yellow solution should be used.

Nominal teicoplanin content of vial	200 mg
Volume of powder vial	10 ml
Volume containing nominal teicoplanin dose (Extracted by 5ml syringe and 23 G needle)	3.0 ml

The reconstituted solution may be injected directly or alternatively further diluted.

Preparation of the diluted solution before infusion:

TICPLAT 200 can be administered in the following infusion solutions:
- sodium chloride 9 mg/mL (0.9%) solution
- Ringer solution
- Ringer-lactate solution
- Glucose injection (5%w/v)
- Glucose injection (10%w/v)
- 0.18% sodium chloride and 4% glucose injection
- 0.45% sodium chloride and 5% glucose injection
- Peritoneal dialysis solution containing 3.86% glucose solution.

Any unused product or waste material should be disposed of in accordance with local requirements.

Manufacturer:
Gufic Biosciences Limited, Unit-2
Survey No.171, N.H.No.8,
Near Grid,
Kabilpore-396424,
Navsari, Gujarat State, India.

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see section Special precaution for disposal and other handling.

Contraindications

Hypersensitivity to teicoplanin or to any of the excipient.

Special warnings and precaution for use

Hypersensitivity reactions

Serious, life-threatening hypersensitivity reactions, sometimes fatal, have been reported with teicoplanin (e.g. anaphylactic shock). If an allergic reaction to teicoplanin occurs, treatment should be discontinued immediately and appropriate emergency measures should be initiated.
Teicoplanin must be administered with caution in patients with known hypersensitivity to vancomycin, as crossed hypersensitivity reactions, including fatal anaphylactic shock, may occur.

However, a prior history of the "Red Man Syndrome" that can occur with vancomycin is not a contraindication to teicoplanin.

Infusion related reactions

In rare cases (even at the first dose), red man syndrome (a complex of symptoms including pruritus, urticaria, erythema, angioneurotic oedema, tachycardia, hypotension, dyspnoea) has been observed.

Stopping or slowing the infusion may result in cessation of these reactions. Infusion related reactions can be limited if the daily dose is not given via bolus injection but infused over a 30-minute period.

Severe bullous reactions

Life-threatening or even fatal cutaneous reactions Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported with the use of teicoplanin. If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present teicoplanin treatment should be discontinued immediately.

Spectrum of antibacterial activity

Teicoplanin has a limited spectrum of antibacterial activity (Gram-positive). It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a high suspicion that the most likely pathogen(s) would be suitable for treatment with teicoplanin.
The rational use of teicoplanin should take into account the bacterial spectrum of activity, the safety profile and the suitability of standard antibacterial therapy to treat the individual patient. On this basis it is expected that in most instances teicoplanin will be used to treat severe infections in patients for whom standard antibacterial activity is considered to be unsuitable.

Loading dose regimen

Since data on safety are limited, patients should be carefully monitored for adverse reactions when teicoplanin doses of 12mg/kg body weight twice a day are administered. Under this regimen blood creatinine values should be monitored in addition to the recommended periodic haematological examination.

Teicoplanin should not be administered by intraventricular use.

Thrombocytopenia
Thrombocytopenia has been reported with teicoplanin. Periodic haematological examinations are recommended during treatment, including complete cell blood count.

Nephrotoxicity

Renal failure has been reported in patients treated with teicoplanin. Patients with renal insufficiency, and/or in those receiving teicoplanin in conjunction with or sequentially with other medicinal products with known nephrotoxic potential (aminoglycosides, colistin, amphotericin B, ciclosporin, and cisplatin) should be carefully monitored, and should include auditory tests.

Since teicoplanin is mainly excreted by the kidney, dose of teicoplanin must be adapted in patients with renal impairment.

Ototoxicity

As with other glycopeptides, ototoxicity (deafness and tinnitus) has been reported in patients treated with teicoplanin. Patients who develop signs and symptoms of impaired hearing or disorders of the inner ear during treatment with teicoplanin should be carefully evaluated and monitored, especially in case of prolonged treatment and in patients with renal insufficiency. Patients receiving teicoplanin in conjunction with or sequentially with other medicinal products with known neurotoxic/ototoxic potential (aminoglycosides, ciclosporin, cisplatin, furosemide and ethacrynic acid) should be carefully monitored and the benefit of teicoplanin evaluated if hearing deteriorates.

Special precautions must be taken when administering teicoplanin in patients who require concomitant treatment with ototoxic and/or nephrotoxic medicinal products for which it is recommended that regular haematology, liver and kidney function tests are carried out.

Superinfection

As with other antibiotics, the use of teicoplanin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Interaction with other medicinal product and other form of interaction:

No specific interaction studies have been performed.

Teicoplanin and aminoglycoside solutions are incompatible and must not be mixed for injection; however, they are compatible in dialysis fluid and may be freely used in the treatment of CAPD-related peritonitis. Teicoplanin should be used with care in conjunction with or sequentially with other medicinal products with known nephrotoxic or ototoxic potential. These include aminoglycosides, colistin, amphotericin B, ciclosporin, cisplatin, furosemide, and ethacrynic acid. However, there is no evidence of synergistic toxicity in combinations with teicoplanin.

Teicoplanin has been administered to many patients already receiving various medications including other antibiotics, antihypertensives, anaesthetic agents, cardiac medicinal products and antidiabetic agents without evidence of adverse interaction.

Paediatric population

Interaction studies have only been performed in adults.

Pregnancy, Lactation and Fertility

Pregnancy

There are a limited amount of data from the use of teicoplanin in pregnant women. Studies in animals have shown reproductive toxicity at high doses: in rats there was an increased incidence of stillbirths and neonatal mortality. The potential risk for humans is unknown.
Therefore, teicoplanin should not be used during pregnancy unless clearly necessary. A potential risk of inner ear and renal damage to the foetus cannot be excluded.

Breast-feeding

It is unknown whether teicoplanin is excreted in human milk. There is no information on the excretion of teicoplanin in animal milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with teicoplanin should be made taking into account the benefit of breast-feeding to the child and the benefit of teicoplanin therapy to the mother.

Fertility

Animal reproduction studies have not shown evidence of impairment of fertility.

Effects on ability to drive and use machines

Teicoplanin has minor influence on the ability to drive and use machines. Teicoplanin can cause dizziness and headache. The ability to drive or use machines may be affected. Patients experiencing these undesirable effects should not drive or use machines.

Undesirable side effects

Tabulated list of adverse reactions

In the table below all the adverse reactions, which occurred at an incidence greater than placebo and more than one patient are listed using the following convention:

Very common; common, uncommon, rare, very rare, not known

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions should be monitored when teicoplanin doses of 12 mg/kg body weight twice a day are administered.

System organ class	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations			Abscess		Superinfection (overgrowth of non-susceptible organisms)
Blood and the lymphatic system disorders		Leucopenia, thrombocytopenia, eosinophilia			Agranulocytosis, neutropenia
Immune system disorders		Anaphylactic reaction (anaphylaxis)			Drug reaction with eosinophilia and systemic symptoms (DRESS), anaphylactic shock
Nervous system disorder s		Dizziness, headache			Seizures
Ear and Labyrinth disorders		Deafness, hearing loss , tinnitus, vestibular disorder			
Vascular disorders		Phlebitis			Thrombophlebitis
Respiratory, thoracic and mediastinal disorders		Bronchospasm			
Gastro - intestinal disorders		Diarrhoea, vomiting, nausea			
Skin and subcutaneous tissue disorders	Rash, erythema, pruritus		Red man syndrome (e.g. Flushing of the upper part of the body)		Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, angioedema, dermatitis exfoliative, urticaria
Renal and Urinary disorders		Blood creatinine increased			Renal failure (including renal failure acute)
General disorders and administration site conditions	Pain, pyrexia				Injection site abscess, chills (rigors)
Investigations		Transaminases increased (transient abnormality of transaminases), blood alkaline phosphatase increased (transient abnormality of alkaline phosphatase), blood creatinine increased (transient rise of serum creatinine)			

Overdose:

Symptoms

Cases of accidental administration of excessive doses to paediatric patients have been reported. In one case agitation occurred in a 29-day-old newborn who had been administered 400 mg intravenously (95 mg/kg).

Management

Treatment of teicoplanin overdose should be symptomatic.

Teicoplanin is not removed by haemodialysis and only slowly by peritoneal dialysis.

Pharmaceutical Properties:

Pharmacodynamic properties:

Pharmacotherapeutic group: Glycopeptide antibacterials, ATC Code: J01XA02

Mechanism of action

Teicoplanin inhibits the growth of susceptible organisms by interfering with cell-wall biosynthesis at a site different from that affected by beta-lactams. Peptidoglycan synthesis is blocked by specific binding to D-alanyl-D-alanine residues.

Mechanism of resistance

Resistance to teicoplanin can be based on the following mechanisms:

- Modified target structure: this form of resistance has occurred particularly in Enterococcus faecium. The modification is based on exchange of the terminal D-alanine-D-alanine function of the amino-acid chain in a murein precursor with D-Ala-D-lactate, thus reducing the affinity to vancomycin. The responsible enzymes are a newly synthesised D-lactate dehydrogenase or ligase.
- The reduced sensitivity or resistance of staphylococci to teicoplanin is based on the overproduction of murein precursors to which teicoplanin is bound.

Cross-resistance between teicoplanin and the glycoprotein vancomycin may occur. A number of vancomycin-resistant enterococci are sensitive to teicoplanin (Van-B phenotype).

Susceptibility testing breakpoints

The MICs breakpoints according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), version 13.0, January 1st, 2023 are displayed in the following table:

Microorganism	MIC Breakpoints (mg/L)	
	Susceptible S ≤	Resistant R >
S. aureus [1]	2	2
Coagulase -negative staphylococci	4	4
Enterococcus spp.	2	2
Streptococcus groups A, B, C, G [1]	2	2
Streptococcus pneumoniae [1]	2	2
Viridans group streptococci [1]	2	2
PK-PD(Non species related) breakpoints	IE	IE

[1]Resistant isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such isolate must be confirmed and the isolate sent to a reference laboratory.

PK-PD indicates Pharmacokinetics-Pharmacodynamics

IE Indicates that there is insufficient evidence that the organism or group is a good target for therapy with agent A MIC with a comment but without an accompanying S, I or R categorization may be reported.

Pharmacokinetic/Pharmacodynamic relationship

Teicoplanin antimicrobial activity depends essentially on the duration of time during which the substance level is higher than the minimum inhibitory concentration (MIC) of the pathogen.

Susceptibility

The prevalence of resistance may vary geographically and over time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some of types of infections is questionable.

Commonly susceptible species
Aerobic Gram -positive bacteria
Corynebacterium jeikeium [a]
Enterococcus faecalis
Staphylococcus aureus (including methicillin -resistant strains)
Streptococcus agalactiae
Streptococcus dysgalactiae subsp. *equisimilis* [a]
(Group C & G streptococci)
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococci in the viridans group [a b]
Anaerobic Gram -positive bacteria
Clostridium difficile [a]
Peptostreptococcus spp.[a]
Species for which acquired resistance may be a problem
Aerobic Gram -positive bacteria
Enterococcus faecium
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Inherently resistant bacteria
All Gram -negative bacteria
Other bacteria
Chlamydia spp.
Chlamydophila spp.
Legionella pneumophila
Mycoplasma spp.
a No current data were available when the tables were published. The primary literature, standard volumes and treatment recommendations assume sensitivity *b* Collective term for a heterogeneous group of streptococcus species. Resistance rate can vary depending on the actual streptococcus species .