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

Teicoplanin injection IP
(Lyophilized)

TICOMYCIN® 200 mg

Each vial contains:
Teicoplanin IP 200 mg
Excipients q.s.

TICOMYCIN® 400 mg

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DESCRIPTION:
Teicoplanin is a mixture of the glycopeptides produced by the growth of certain strains of Actinoplanes teichomyceticus sp. fermentation product. The 6 principle contents of the mixture are teicoplanin A2-1 to A2-5 and teicoplanin A3-1.

THERAPEUTIC INDICATIONS
Teicoplanin is indicated in adults and in children from birth for the parenteral treatment of the following infections (see Posology and Method of Administration, Special Warnings and Precautions for use):
- 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),
- bacteremia that occurs in association with any of the indications listed above.

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
The standard dose of 400mg equates to approximately 6mg/kg. In patients weighing more than 85kg, a dose of 6mg/kg should be used.

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	6 mg/kg body weight intravenous or intramuscular once a day	>15 mg/L once a week
Bone and joint infections	12 mg/kg body weight every 12 hours for 3 to 5 intravenous administrations	>20 mg/L	12 mg/kg body weight Intravenous or intramuscular once a day	>20 mg/L
Infective endocarditis	12 mg/kg body weight every 12 hours for 3 to 5 Intravenous administrations	30-40 mg/L	12 mg/kg body weight Intravenous or intramuscular once a day	>30 mg/L

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 (see below).
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 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 haemodialysis.
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. 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.
Method of reconstitution:
This medicinal product is for single use only.
Preparation of reconstituted solution:
- Slowly inject the entire content of the water for injection into the powder vial.
- Gently roll the vial between the hands until the powder is completely dissolved.

If the solution does become foamy, then it should be left to stand for about 15 minutes. Only clear and yellowish solutions should be used.
The reconstituted solutions will contain 100 mg of teicoplanin in 1.5 mL, 200 mg in 3.0 mL and 400 mg in 3.0 mL.
The final solution is isotonic with plasma and has a pH of 7.2-7.8.

Nominal teicoplanin content of vial	100 mg	200 mg	400 mg
Volume of powder vial	8 mL	10 mL	22 mL
Volume withdrawable from the solvent ampoule for reconstitution	1.8 mL	3.2 mL	3.2 mL
Volume containing nominal teicoplanin dose (extracted by 5 mL syringe and 23 G needle)	1.5 mL	3.0 mL	3.0 mL

The reconstituted solution may be injected directly or alternatively further diluted.
Preparation of the diluted solution before infusion:
Teicoplanin 100mg can be administered in the following infusion solutions:
- Sodium chloride 9 mg/mL (0.9%) solution
- Ringer solution
- Hartmanns Solution (Compound Sodium Lactate solution)
- 5% dextrose injection
- 0.18% sodium chloride and 4% glucose solution
- Peritoneal dialysis solution containing 1.36% or 3.86% glucose solution.

CONTRAINDICATIONS
Hypersensitivity to the active substance (teicoplanin) or to any of the excipients used in formulation.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Teicoplanin should not be administered by intraventricular use.
Hypersensitivity reactions: 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 "red man syndrome" with vancomycin is not a contraindication to the use of 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 cutaneous adverse reactions: Severe cutaneous adverse reactions (SCAR) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal have been reported with the use of teicoplanin (see Undesirable effects). Acute generalized exanthematous pustulosis (AGEP) has also been reported with the use of teicoplanin (see Undesirable effects). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions (e.g. progressive skin rash often with blisters or mucosal lesions or pustular rash, or any other sign of skin hypersensitivity) and be closely monitored. If signs and symptoms suggestive of severe skin reactions appear, teicoplanin should be withdrawn and alternative treatment should be considered.
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.
Thrombocytopenia: Thrombocytopenia has been reported with teicoplanin (see Undesirable effects). Periodic haematological examinations, including complete blood count, are recommended during treatments.
Nephrotoxicity: Nephrotoxicity and renal failure have been reported in patients treated with teicoplanin (see Undesirable Effects). Patients with renal insufficiency, in those receiving the high loading dose regimen of teicoplanin, and those receiving teicoplanin in conjunction with or sequentially with other medicinal products with known nephrotoxic potential (e.g. aminoglycosides, colistin, amphotericin B, ciclosporin, and cisplatin) should be carefully monitored, and should get auditory tests (see "Ototoxicity" below).
Since teicoplanin is mainly excreted by the kidney, the dose of teicoplanin must be adapted in patients with renal impairment (see Posology and Method of Administration).

Ototoxicity: As with other glycopeptides, ototoxicity (deafness and tinnitus) has been reported in patients treated with teicoplanin (see Undesirable Effects). 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 nephrotoxic and/or neurotoxic/ototoxic potential (e.g. aminoglycosides, colistin, amphotericin B, 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 PRODUCTS AND OTHER FORMS OF INTERACTION
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 and/or neurotoxic/ototoxic potential. These include e.g. aminoglycosides, colistin, amphotericin B, ciclosporin, cisplatin, furosemide, and ethacrynic acid (see Special Warnings and Precautions for use).
However, there is no evidence of synergistic toxicity in combinations with teicoplanin.

PREGNANCY, LACTATION AND FERTILITY
Pregnancy: 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 (see Special Warnings and Precautions for use).
Lactation: It is unknown whether teicoplanin is excreted in human 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.

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 EFFECTS
Infections and infestations: Abscess, Superinfection (overgrowth of nonsusceptible organisms)
Blood and the lymphatic system disorders: Leucopenia, thrombocyte penia, eosinophilia, Agranulocytosis, neutropenia, pancytopenia
Immune system disorders: Anaphylactic reaction (anaphylaxis) (see Special Warnings and Precautions for use), Drug reaction with eosinophilia and systemic symptoms (DRESS), anaphylactic shock (see Special Warnings and Precautions for use)
Nervous system disorders: Dizziness, headache, Seizures
Ear and labyrinth disorders: Deafness, hearing loss (see Special Warnings and Precautions for use), tinnitus, vestibular disorder
Vascular disorders: Phlebitis, Thrombophlebitis
Respiratory, thoracic and mediastinal disorders: Bronchospasm
Gastrointestinal disorder: Diarrhoea, Vomiting, Nausea
Skin and subcutaneous tissue disorders: Rash, erythema, pruritus, Red man syndrome (e.g. Flushing of the upper part of the body) (see Special Warnings and Precautions for use), Toxic epidermal necrolysis, Stevens Johnson syndrome, acute generalized exanthematous pustulosis, erythema multiforme, angioedema, dermatitis exfoliative, urticaria (see Special Warnings and Precautions for use)
Renal and urinary disorders: Blood creatinine increase, 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)

OVERDOSE
Symptoms: Cases of accidental administration of excessive doses to paediatric patients have been reported.
Management: Treatment of teicoplanin overdose should be symptomatic. Teicoplanin is not removed by haemodialysis and only slowly by peritoneal dialysis.

PHARMACOLOGICAL 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).
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.
Pharmacokinetic 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 (V_{ss}) varies from 0.7 to 1.4 ml/kg. The highest values of V_{ss} 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 faeces (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.

STORAGE:
Store below 25ºC Vial should be protected from heat & light.
After reconstitution: 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 and would normally not be longer than 24 hours at 2 to 8ºC.

PRESENTATION:
TICOMYCIN 200/400
Primary packing: 10 ml clear tubular glass vial USP type-I.
Secondary packing: Each vial placed on tray, packed in printed monocarton along with package insert.

Marketed By:
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