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

This package insert is continually updated: Please read carefully before using a new pack.

Teicoplanin Injection IP
Targocid® I.M. / I.V.

DESCRIPTION

Active Ingredient
Teicoplanin

Therapeutic Or Pharmacological Class
Pharmacotherapeutic group: Glycopeptide antibacterials, ATC code: J01XA 02

Pharmaceutical Form
Sterile powder for injection/infusion

COMPOSITION
Targocid® 200mg - Each vial contains (as lyophilisate) Teicoplanin I.P. 200mg
Targocid® 400mg - Each vial contains (as lyophilisate) Teicoplanin I.P. 400mg.

INDICATIONS

In serious gram +ve infections, serious staphylococcal infections in patients sensitive or unresponsive to penicillins and cephalosporins, CAPD related peritonitis, prophylaxis in orthopaedic surgery at risk of gram +ve infections.

DOSAGE AND ADMINISTRATION

Adults:
For most gram-positive infections: loading regimen of three 12-hourly doses of 400 mg IV, followed by a maintenance dose of 400 mg IV or IM once daily. The standard dose of 400 mg equates to approximately 6 mg/kg. In patients weighing more than 85 kg, a dose of 6 mg/kg should be used.

Higher doses may be required in some clinical situations.

Surgical Prophylaxis: 400 mg (or 6 mg/kg if >85 kg) IV single dose at time of anesthesia induction.

Pediatrics:
>2 months to 16 years: For most gram-positive infections: loading regimen of three 12-hourly doses of 10 mg/kg IV, followed by a maintenance dose of 6 mg/kg IV or IM once daily.

Severe infections and infections in the neutropenic patient: Loading regimen of three 12-hourly doses of 10 mg/kg IV, followed by 10 mg/kg IV once daily.

<2 months: A single loading dose of 16 mg/kg IV the first day, followed by 8 mg/kg IV once daily. The IV dose should be infused over 30 minutes.

Elderly:
No dose adjustment required, unless there is renal impairment (see below).

Renal impairment
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 (measured by HPLC), or 15 mg/L (measured by FPIA) method.
After the 4th day of treatment:

- mild renal insufficiency (Cr Cl between 40 to 60 mL/min): maintenance dose should be halved, either by administering the usual recommended dose every 2 days, or administering one-half the dose daily.

- renal insufficiency (Cr Cl <40 mL/min) and in hemodialyzed patients: maintenance dose should be one-third the usual recommended dose, either by administering the dose every third day, or administering one-third of the dose daily. Teicoplanin is not removed by hemodialysis .

Continuous ambulatory peritoneal dialysis for peritonitis: After a single loading dose of 400 mg IV, 20 mg/L is administered per bag in the first week, 20 mg/L in alternate bags in the second week, then 20 mg/L in the overnight dwell bag during the 3rd week .

ADMINISTRATION

Teicoplanin may be given IV or IM. The IV dose may be administered as a rapid injection over 3 to 5 minutes or as an infusion over 30 minutes. Only the infusion method should be used in neonates Severity of illness and infection site need to be considered in selecting teicoplanin doses.

CONTRAINDICATIONS

Teicoplanin is contraindicated in patients who have exhibited previous hypersensitivity to teicoplanin or any of the excipients.

WARNINGS

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 "red man syndrome" with vancomycin is not a contraindication to the use of teicoplanin.

Infusion related reactions

"Red man syndrome" (a complex of symptoms including pruritus, urticaria, erythema, angioneurotic oedema, tachycardia, hypotension, dyspnoea) has been rarely observed (even at the first dose).
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 (SCARs)

Life-threatening and fatal cutaneous reactions, including Stevens-Johnson syndrome (SJS) Toxic Epidermal Necrolysis (TEN) and Drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of teicoplanin. Acute generalized exanthematous pustulosis (AGEP) has also been reported. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. If symptoms or signs of SJS, TEN, DRESS or AGEP (e.g. progressive skin rash often with blisters or mucosal lesions or pustular rash, or any other sign of skin hypersensitivity) are present teicoplanin treatment should be discontinued immediately.

Nephrotoxicity

Nephrotoxicity and renal failure have been reported in patients treated with teicoplanin (see section Adverse reactions). Patients with renal insufficiency, patients receiving the high loading dose regimen of teicoplanin, and patients receiving teicoplanin in conjunction with or sequentially with other medicinal products with known nephrotoxic potential should be carefully monitored.

Other monitoring

Hearing, hematologic, and hepatic, toxicities have been reported with teicoplanin (see section Adverse reactions). Appropriate monitoring of hearing, hematologic and liver function should be done, particularly in patients with renal insufficiency, patients receiving prolonged therapy or high doses, or patients who receive concurrent ototoxic or nephrotoxic drugs **(**see Section INTERACTIONS)**.**

Intraventricular use
Teicoplanin should not be administered by intraventricular route, due to the risk of seizure.

PRECAUTIONS

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.

Superinfection: As with other antibiotics, the use of teicoplanin, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

INTERACTIONS
Due to the potential for increased adverse effects, teicoplanin should be administered with caution in patients receiving concurrent nephrotoxic or ototoxic drugs, such as aminoglycosides, amphotericin B, ciclosporin, and furosemide.

PREGNANCY
Teicoplanin should not be used during confirmed or presumed pregnancy unless a physician considers that the potential benefits outweigh any possible risk.
Animal reproduction studies have not shown evidence of teratogenic effects.

LACTATION
Information about the excretion of teicoplanin in human breast milk is not known.
Therefore, teicoplanin should not be used during lactation unless a physician considers that the potential benefits outweigh any possible risk.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

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.

ADVERSE REACTIONS

The following CIOMS frequency rating is used, when applicable:
Very common ≥ 10 %; Common ≥ 1 and <10 % ; Uncommon ≥ 0.1 and < 1 %;
Rare ≥ 0.01 and < 0.1 %; Very rare < 0.01 %, Not known (cannot be estimated from available data).

General disorders and administration site conditions
erythema , local pain , thrombophlebitis, injection site abscess with I.M. injection .

Immune system disorders
Hypersensitivity: rash , pruritus , fever , rigors , bronchospasm , anaphylactic reactions, anaphylactic shock (see Section WARNINGS), urticaria , angioedema, DRESS syndrome (drug reaction with eosinophilia and systemic symptoms), exfoliative dermatitis , toxic epidermal necrolysis , erythema multiforme, Stevens Johnson syndrome, Acute generalized exanthematous pustulosis (see Section WARNINGS).

In addition, infusion-related events, called "red man syndrome" (see Section WARNINGS) , have been rarely reported in which the events occurred without a history of previous teicoplanin exposure and did not

recur on reexposure when the infusion rate was slowed and/or the concentration decreased . These events were not specific to any concentration or rate of infusion.

Gastrointestinal disorders
nausea , vomiting , diarrhea.

Blood and lymphatic system disorders
rare cases of reversible agranulocytosis , leucopenia , neutropenia , thrombocytopenia (see Section WARNINGS), eosinophilia.

Liver disorders
increases in serum transaminases and/or serum alkaline phosphatase(see Section WARNINGS).

Renal and urinary disorders
elevations of serum creatinine , renal failure (see Section WARNINGS).
Based on literature reports, the estimated rate of nephrotoxicity in patients receiving low loading dose regimen of average 6 mg/kg twice a day, followed by a maintenance dose of average 6 mg/kg once daily, is around 2%.
In an observational post-authorisation safety study which enrolled 300 patients with a mean age of 63 years (treated for bone and joint infection, endocarditis or other severe infections) who received the high loading dose regimen of 12 mg/kg twice a day (receiving 5 loading doses as a median) followed by a maintenance dose of 12 mg/kg once daily, the observed rate of confirmed nephrotoxicity was 11.0% (95% CI = [7.4%; 15.5%]) over the first 10 days. The cumulative rate of nephrotoxicity from the start of treatment up to 60 days after the last dose was 20.6% (95% CI = [16.0%; 25.8%]).
In patients receiving more than 5 high loading doses of 12 mg/kg twice a day, followed by a maintenance dose of 12 mg/kg once daily, the observed cumulative rate of nephrotoxicity from the start of treatment up to 60 days after the last administration was 27% (95% CI = [20.7%; 35.3%]).

Nervous system disorders
dizziness , headache , seizures .

Ear and labyrinth disorders
hearing loss/deafness (see section WARNINGS), tinnitus , vestibular disorder

Infections and infestations
superinfection (overgrowth of non-susceptible organisms) .

OVERDOSAGE

Signs and Symptoms
Human Experience:

Cases of excessive doses administered in error to pediatric patients have been reported. In one report, agitation occurred in a 29-day-old newborn given 400 mg I.V. (95 mg/kg). In the other cases, there were no symptoms or laboratory abnormalities associated with teicoplanin. In these cases, the ages ranged from 1 month to 8 years. When reported, teicoplanin doses ranging from 35.7 mg/kg to 104 mg/kg were administered in error.

Management:
Treatment of overdosage should be symptomatic. . Teicoplanin is not removed by hemodialysis and only slowly by peritoneal dialysis.

PHARMACODYNAMIC CHARACTERISTICS

PHARMACOKINETICS

Absorption
Teicoplanin is administered by parenteral injection. The bioavailability of a single 3 to 6 mg/kg intramuscular injection is over 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 an intravenous loading dose of 6mg/kg administered 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 6mg/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.

Distribution
The drug distributes readily into skin (subcutaneous fat) and blister fluid , myocardium , pulmonary tissue and pleural fluid , bone and synovial fluid but not readily into cerebrospinal (CSF) fluid . It is 90% to 95% bound with weak affinity to plasma proteins . Steady-state volume of distribution after 3 to 6 mg/kg intravenously ranges from 0.94 L/kg to 1.4 L/kg.

Metabolism
When administered parenterally, the metabolic transformation is minor, about 3% ; about 80% of administered drug is excreted in the urine . Renal clearance after 3 to 6 mg/kg intravenously ranges from 10.4 to 12.1 mL/hr/kg .

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 parenteral administration.
Following intravenous administration of 3 to 6 mg/kg, the plasma concentration declines with a terminal elimination half-life of about 150 hours ; total plasma clearance ranges from 11.9 mL/hr/kg to 14.7 mL/hr/kg . This long half-life allows once a day administration. At 6 mg/kg administered intravenously at 0, 12, 24 hours and every 24 hours thereafter as a 30 minute infusion, a predicted trough serum concentration of 10 mg/L would be reached by Day 4 . Predicted steady state peak and trough serum concentrations of approximately 64 mg/L and 19 mg/L, respectively, would be attained by Day 28 .

Special Populations
Elderly patients
In the elderly population the teicoplanin pharmacokinetics is not modified unless in case of renal impairment.
Pediatric patients
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.
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.

NON-CLINICAL SAFETY DATA

Teratogenicity
Animal reproduction studies have not shown evidence of teratogenic effects.
Impairment of Fertility
Animal reproduction studies have not shown evidence of impairment of fertility

INCOMPATIBILITIES/ COMPATIBILITIES

Soluations of teicoplanin and aminoglycosides are incompatible when mixed directly and should not be mixed before injection.

STORAGE CONDITIONS AND SHELF LIFE

Teicoplanin powder is stable for 3 years when stored below 25°C. The vials should be protected from heat.
Reconstituted solutions should be stored under refrigeration (5°C) and solutions stored for longer than 24 hours be discarded.

PREPARATION AND HANDLING:

SLOWLY inject the prescribed amount of sterile water down the side of the vial.

GENTLY roll the vial between the hands until the powder is completely dissolved, paying attention to avoid the formation of foam. IT IS IMPORTANT TO ENSURE THAT ALL THE POWDER IS DISSOLVED, EVEN THAT NEAR THE STOPPER.

Shaking this solution will cause the formation of foam which will make it difficult to recover the required volume. Nevertheless, if teicoplanin has been completely dissolved the foam does not change the concentration of the solution which will remain 100 mg in each 1.5 mL, 200 mg in 3.0 mL (from the 100 mg and 200 mg vials) or 400 mg in 3.0 mL (from the 400 mg vial). If the solution does become foamy, then it should be left to stand for about 15 minutes.

Withdraw the teicoplanin solution slowly from the vial, trying to recover most of it by placing the needle in the central part of the rubber stopper.
The reconstituted solutions will contain 100 mg of teicoplanin in 1.5 mL, 200 mg in 3.0 mL (from the 100 mg and 200 mg vials), and 400 mg in 3.0 mL (from the 400 mg vial).
It is important that the solution is correctly prepared and carefully withdrawn into the syringe; preparations that are not carefully executed can lead to the administration of less than the full dose.

The final solution is isotonic with plasma and has a pH of 7.2-7.8.
The reconstituted solution may be injected directly or alternatively further diluted (see table below).
As a matter of good pharmaceutical practice, these solutions should be used immediately after admixing.

Diluent	Final Teicoplanin Concentration (mg/mL)
0.9% sodium chloride injection	1, 2, 10, 16
5% dextrose injection	2, 4, 10
5% dextrose - 0.45% sodium chloride injection	2, 4
Lactated Ringers' injection	2, 4
Compound sodium lactate injection (Hartmann's)	2
0.18% sodium chloride and 4% dextrose injection	2
Peritoneal dialysis solution containing 1.36% or 3.86% dextrose	0.1

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