## 1. Trade Name of the Medicinal Product

Targocid 200mg

## 2. Qualitative and Quantitative Composition

Teicoplanin 200mg

## 3. Pharmaceutical Form

Powder for Injection

## 4. Clinical Particulars

4.1 Therapeutic Indications

*Staphylococcus* infective endocarditis, osteomyelitis, pneumonia, septicaemia, soft tissue infections, enteritis and *Clostridium difficile* infective pseudomembranous colitis.

Explanation:
Targocid is indicated in potentially serious Gram-positive infections including those which cannot be treated with other antimicrobial drugs, eg. penicillins and cephalosporins.
Targocid is useful in the therapy of serious staphylococcal infections in patients who cannot receive or who have failed to respond to the penicillins and cephalosporins, or who have infections with staphylococci resistant to other antibiotics.

The effectiveness of teicoplanin has been documented in the following infections:
Skin and soft tissue infections, urinary tract infections, lower respiratory tract infections, joint and bone infections, septicaemia, endocarditis and peritonitis related to continuous ambulatory peritoneal dialysis.

4.2 Posology and Method of Administration

GENERAL

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.

Adults

- Treatment of Gram positive infections

| ***Indications*** | **Loading dose** | | **Maintenance dose** | |
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| | **Loading dose regimen** | **Targeted trough concentrations at day 3 to 5** | **Maintenance dose** | **Targeted trough concentrations during maintenance** |
| - lower respiratory tract infection<br>- skin and soft tissue infections<br>- complicated urinary tract infections (urosepsis)<br>- bacteraemia | 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 |

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| that occurs in association with any of the indications listed, sepsis/septicemia | | | | |
| - 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.

The duration of treatment should be decided based on the clinical response. For infective endocarditis a minimum of 21 days is usually considered appropriate.

Measurements of serum concentrations[1]

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.

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

- Infection-associated diarrhea and colitis caused by Clostridium difficile: 100-200 mg orally twice daily for 7 to 14 days daily.

**SPECIAL POPULATIONS**

***Children***

Children 2 months to 16 years:

For most gram-positive infections: loading regimen of three 12 hourly doses of 10 mg/kg body weight IV, followed by a maintenance dose of 6 mg/kg body weight IV or IM once daily .

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

Neonates and infants up to the age of 2 months:

A single loading dose of 16 mg/kg body weight IV the first day, followed by one single dose of 8 mg/kg body weight 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.
For *Clostridium difficile* infection-associated diarrhea and colitis, the oral route is to be used.

4.3 Contra-Indications
Teicoplanin is contra-indicated in patients who have exhibited previous hypersensitivity to the drug.

4.4 Special Warnings and Special Precautions for Use
Warnings:
**Hypersensitivity reaction**
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 hypersensitive to vancomycin, as crossed hypersensitivity reactions, including fatal anaphylactic shock, may occur. However, a prior history of the "Red Man Syndrome" with vancomycin is not a contra-indication to the use of teicoplanin.

**Infusion related reactions**
"Red man syndrome" 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-minutes 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 are present teicoplanin treatment should be discontinued immediately.

**Monitoring**
Hearing, hematologic, hepatic, and renal toxicities have been reported with teicoplanin. Appropriate monitoring of hearing, hematologic, liver, and renal function should be done, particularly in patients with renal insufficiency, patients receiving prolonged therapy, or patients who receive concurrent ototoxic or nephrotoxic drugs.

**Loading dose regimen**
Patients should be carefully monitored for adverse reactions when teicoplanin loading doses of 12mg/kg body weight twice a day are administered. Blood creatinine values should be monitored in addition to the recommended periodic haematological examination.

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

Precautions:
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.

4.5 Interaction With Other Medicaments and Other Forms of Interaction

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, ethacrynic acid, cisplatin, colistin.

4.6 Pregnancy and Lactation

Animal reproduction studies have not shown evidence of impairment of fertility or teratogenic effect. At high doses in rats there was an increased incidence of stillbirths and neonatal mortality. It is recommended that teicoplanine should not be used during confirmed or presumed pregnancy or during lactation unless a physician considers that the potential benefits outweigh a possible risk. Information about the excretion of teicoplanin in human breast milk is not known.

4.7 Effects on Ability to Drive and Use Machines

Teicolpanin can cause dizziness and headache. The ability to drive or use machines may be affected.

4.8 Adverse reactions

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

Hypersensitivity: rash, pruritus, fever, rigors, bronchospasm, anaphylactic reactions, anaphylactic shock, urticaria, angioedema, DRESS syndrome (drug reaction with eosinophilia and systemic symptoms), exfolative dermatitis, toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson Syndrome.

In addition, infusion-related events, called “red man syndrome” have been rarely reported in which the events occurred without a history of previous teicoplanin exposure and did not recur on re-exposure when the infusion rate was slowed and/or concentration decreased. These events were not specific to any concentration or rate of infusion.

Gastric-intestinal: nausea, vomiting, diarrhoea.

Blood: eosinophilia, leucopenia, thrombocytopenia, neutropenia, rare cases of reversible agranulocytosis.

Liver function: increases in serum transaminases and/or serum alkaline phosphatase.

Renal function: elevations of serum creatinine, renal failure.

Central nervous system: dizziness, headache, seizures.

Auditory/vestibular: hearing loss/ deafness, tinnitus and vestibular disorder.

Other: Superinfection (overgrowth of non-susceptible organisms).

4.9 Overdose

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 400mg I.V. (95 mg/kg). In the other cases, there were no symptoms or laboratory abnormalities associated with teicoplanin.

Teicoplanin is not removed by haemodialysis and only by peritoneal dialysis. Treatment of overdosage should be symptomatic.

## 5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Teicoplanin is a bactericidial, glycopeptide antibiotic, produced by fermentation of Actinoplanes teichomyceticus. It is active against both aerobic and anaerobic Gram-positive bacteria.

Species usually sensitive (MIC less than or equal to 16mg/1):
Staphylococcus aureus and coagulase negative staphylococci (sensitive or resistant to methicillin), streptococci, enterococci, Listeria monocytogenes, micrococci, Eikenella corrodens, group JK corynebacteria and Gram-positive anaerobes including Clostridium difficile, and peptococci.

Species usually resistant (MIC superior to 16mg/1):
Nocardia asteroides, Lactobacillus spp, Leuconostoc and all Gram-negative bacteria.

Bactericidal synergy has been demonstrated in vitro with aminoglycosides against group D streptococci and staphylococci. In vitro combinations of teicoplanin with rifampicin or fluorinated quinolones show primarily additive effects and sometimes synergy.

One-step resistance to teicoplanin could not be obtained in vitro and multi-step resistance was only reached in vitro after 11-14 passages.

Teicoplanin does not show cross-resistance with other classes of antibiotics.

The use of teicoplanin may result in overgrowth of non-susceptible organisms. If new infections due to bacteria or fungi appear during treatment appropriate measures should be taken.

Susceptibility testing:
Sensidiscs are charged with 30 micrograms of teicoplanin. Strains showing an inhibition zone diameter of 14mm or more are susceptible and those of 10mm or less are resistant.

5.2 Pharmacokinetic Properties

Following injection teicoplanin rapidly penetrates into tissues, including skin, fat and bones and reaches the highest concentrations in the kidney, trachea, lungs and adrenals. Teicoplanin does not readily penetrate into the cerebro-spinal fluid (CSF).

In man the plasma level profile after intravenous administration indicates a biphasic distribution (with a rapid distribution phase having a half-life of about 0.3 hours, followed by a more prolonged distribution phase having a half-life of about 3 hours), followed by slow elimination (with a terminal elimination half-life of about 150 hours). At 6mg/kg administered intravenously at 0, 12, 24 hours and every 24 hours thereafter as a 30 minute infusion, a predicted trough serum concentration of 10mg/L would be reached by Day 4. The steady state volume of distribution after 3 to 6mg/kg intravenously ranges from 0.94 L/kg to 1.4 L/kg. The volume of distribution in children is not substantially different from that in adults.

Approximately 90-95% teicoplanin is bound with weak affinity to plasma proteins. Teicoplanin penetrates readily into blister exudates and into joint fluid; it penetrates neutrophils and enhances their bactericidal activity; it does not penetrate red blood cells.

No metabolites of teicoplanin have been identified; more than 97% of the administered teicoplanin is excreted unchanged. The elimination of teicoplanin from the plasma is prolonged with a terminal half-life of elimination in man of about 150 hours. Teicoplanin is excreted mainly in the urine.

5.3 Preclinical Safety Data
Not Applicable

## 6. Pharmaceutical Particulars

6.1 List of Excipients
Sodium chloride

6.2 Incompatibilities
Solutions of teicoplanin and aminoglycosides are incompatible when mixed directly and should not be mixed before injection.

6.3 Shelf-life
3 years unopened.
24 hours after reconstitution.

6.4 Special Precautions for Storage
Finished Product:
Vials of dry Targocid should not be stored above 25$^{o}$C.

Reconstituted Product:
In keeping with good clinical pharmaceutical practise reconstituted vials of Targocid should be used immediately and any unused portion discarded. On the few occasions when changing circumstances make this impractical reconstituted solutions should be kept at 2 - 8$^{oC}$ and discarded within 24 hours. Do not store in a syringe.

6.5 Nature and Contents of Container
Colourless, BP, Type I glass vials, closed with a butyl rubber plug and combination aluminium/plastic “flip-off cap” (colour coded yellow).
Pack size: 1 vial

6.6 Instructions for Use/Handling
Preparation of Injection
The entire contents of the water ampoule should be slowly added to the vial of Targocid and the vial rolled gently until the powder is completely dissolved, taking care to avoid formation of foam. If the solution does become foamy then allow to stand for about 15 minutes for the foam to subside.

A calculated excess is included in each vial of Targocid so that, when prepared as described above, a full dose of 100mg, 200mg or 400mg (depending on the strength of the vial) will be obtained if all the reconstituted solution is withdrawn from the vial by a syringe. The concentration of teicoplanin in these injections will be 100mg in 1.5ml (from the 100mg and 200mg vials).
The reconstituted solution may be injected directly, or alternatively diluted with:
• 0.9% Sodium Chloride Injection
• Compound Sodium Lactate Injection (Ringer-Lactate Solution, Hartmanns Solution)
• 5% Dextrose Injection
• 0.18% Sodium Chloride and 4% Dextrose Injection
• Peritoneal dialysis solution containing 1.36% or 3.86% Dextrose.

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