

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Targocid 400 mg lyophilised powder for injection with water for injections ampoule.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 400mg teicoplanin equivalent to not less than 400,000 IU.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Teicoplanin lyophilised powder for injections is an off-white, odourless powder contained in a vial of 20 mL (400 mg) together with ampoules of water for injections.

The final solution is isotonic with plasma and has a pH of 7.2 -7.8. See section 6.6.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Targocid is indicated in adults and in children from 2 months for the treatment of the following serious infections due to staphylococci or streptococci, which cannot be treated satisfactorily with less toxic agents including beta-lactam antibiotics:-

Bone - osteomyelitis

Joint - septic arthritis

Blood - non-cardiac bacteraemia, septicaemia

4.2 DOSE AND METHOD OF ADMINISTRATION

Teicoplanin can be administered either intravenously or intramuscularly. Intravenous dosing may be by rapid injection over 3-5 minutes, or more slowly over a 30 minute infusion. An intramuscular injection of teicoplanin should not exceed 3 mL (400 mg) at a single site. For instructions on reconstitution of the medicine before administration see Section 6.6.

Dosage is usually once daily following an initial loading dose which is administered as three 12-hourly doses on the first day of therapy. The dose is to be adjusted on body weight whatever the weight of the patient.

The majority of patients with infections caused by organisms sensitive to the antibiotic show a therapeutic response within 48-72 hours. The total duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. The following periods are often appropriate:

- Uncomplicated bacteraemia 2-4 weeks
- Septic arthritis or osteomyelitis 3-6 weeks

The use of teicoplanin may result in overgrowth of non-susceptible organisms.

Adults

Septicaemia/bacteraemia, acute or chronic osteomyelitis

Treatment should be started with 6 mg/kg by the I.V. route every 12 hours for 3 doses then the daily maintenance dose should be 6 mg/kg once daily. Higher doses may be required in some clinical situations.

Septic Arthritis

Patients with septic arthritis should receive 12mg/kg, intravenously, every 12 hours for 3 doses then a daily maintenance dose of 12mg/kg.

Paediatric Patients

Children aged 2 months to 16 years: for severe infections and infections in neutropenic patients, the recommended dose is 10mg/kg intravenously, every 12 hours for the first three doses; thereafter a dose of 10mg/kg should be administered intravenously as a single dose, once daily.

For moderate infections, the recommended dose is 10mg/kg intravenously, every 12 hours for the first three doses; thereafter a dose of 6mg/kg should be administered by either intravenous or intramuscular injection as a single dose, once daily.

Elderly Patients

No dosage adjustment required unless renal function is impaired. The instructions for impaired renal function should then be followed.

Patients with Renal Impairment

For patients with impaired renal function, reduction of dosage is not required until the fourth day of Targocid[®] treatment. Trough plasma teicoplanin concentrations should be monitored

periodically after the first week of therapy and the dosage adjusted to prevent trough concentrations exceeding 30 µg/mL in patients with septic arthritis or 15 µg/mL in other cases, with a minimum of 10 µg/mL.

In mild renal insufficiency (creatinine clearance between 40 and 60 mL/min)

From the fourth day of treatment the Targocid® 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 40 mL/min, and in haemodialysed patients)

From the fourth day of treatment the Targocid® dose should be reduced to one third of the normal dose either by administering the dose every third day, or by administering one third of this dose once a day.

Teicoplanin is not appreciably removed by haemodialysis or peritoneal dialysis.

Combination Therapy

Combination with an appropriate bactericidal agent is recommended when mixed infection with a gram-negative pathogen cannot be excluded (e.g. empiric therapy of fever in neutropenic patients).

4.3 CONTRAINDICATIONS

Teicoplanin is contraindicated in patients who have exhibited previous hypersensitivity to teicoplanin.

4.4 SPECIAL WARNINGS AND PRECAUTIONS 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 of known hypersensitivity to vancomycin since cross hypersensitivity reactions, including fatal anaphylactic shock, may occur.

However, a history of 'Red Man Syndrome' with vancomycin is not a contraindication to 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 bullous reactions

Life-threatening or even fatal cutaneous reactions such as 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 (eg progressive skin rash often with blisters or mucosal lesion) are present, teicoplanin treatment should be discontinued immediately.

Monitoring

Hearing, haematologic, hepatic and renal toxicities have been reported with teicoplanin. Appropriate periodic haematological studies, auditory, renal and liver function tests should be conducted, particularly during prolonged therapy and when administering teicoplanin to:

- patients with renal insufficiency,
- patients who require concurrent use of drugs which may have ototoxic and/or nephrotoxic properties (aminoglycosides, colistin, amphotericin B, ciclosporin, cisplatin, furosemide (frusemide) and etacrynic acid).

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. Under this regimen 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.

Superinfection

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 MEDICINES AND OTHER FORMS OF INTERACTION

Animal studies have shown lack of interaction with diazepam, thiopentone, morphine, neuromuscular blocking agents or halothane.

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 (frusemide).

Solutions of teicoplanin and aminoglycosides are incompatible and should not be mixed before injection. See section 6.2.

4.6 FERTILITY, PREGNANCY AND LACTATION

Category B3.

Although animal reproduction studies have not shown evidence of impairment of fertility or teratogenic effects, teicoplanin should not be used during confirmed or presumed pregnancy or during lactation unless a physician considers that the potential benefits outweigh any possible risk. Information about the excretion of teicoplanin in milk or placental transfer of the drug is not known.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Teicoplanin can cause dizziness and headache. The ability to drive or operate machinery may be affected. Patients experiencing these undesirable effects should not drive or operate machinery.

4.8 UNDESIRABLE EFFECTS

Teicoplanin is generally well tolerated. Adverse reactions rarely require cessation of therapy and are generally mild and transient. Serious side effects are rare. The following have been reported, but a causal effect has not been established in all cases:

Infections and Infestations: superinfection (overgrowth of non-susceptible organisms)

Blood and lymphatic system disorders: eosinophilia, leucopenia, neutropenia, thrombocytopenia and rare cases of reversible agranulocytosis.

Immune system disorders: rash, pruritus, fever, bronchospasm, anaphylactic reactions, anaphylactic shock, rigors, urticaria, angioedema and rare reports of exfoliative dermatitis, DRESS syndrome (drug reaction with eosinophilia and systemic symptoms), toxic epidermal necrolysis, erythema multiforme including Stevens-Johnson syndrome.

Nervous system disorders: dizziness and headache, seizures with intraventricular use.

Ear and labyrinth disorders: hearing loss/deafness, tinnitus, vertigo and other vestibular disorders.

Gastrointestinal disorders: nausea, vomiting, diarrhoea.

Hepatobiliary disorders: increases in serum transaminases and/or serum alkaline phosphatase.

Renal and urinary disorders: transient elevations of serum creatinine, renal failure.

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

In addition, infusion-related events called “red man syndrome” such as erythema or flushing of the upper body, have been rarely reported (see section 4.4). These events occurred without a history of previous teicoplanin exposure and did not recur on re-exposure when the infusion rate was slowed and/or the concentration was decreased. These events were not specific to any concentration or rate of infusion.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 OVERDOSE

Cases of excessive doses administered in error to paediatric patients have been reported. In one report, agitation occurred in a 29 day-old newborn given 400mg I.V. (95mg/kg). In the other cases, there were no symptoms or laboratory abnormalities associated with teicoplanin.

Treatment of overdosage should be symptomatic. Haemodialysis does not remove the drug. Overdoses of 100 mg/kg/day have been administered in error to neutropenic paediatric patients. Despite high plasma concentrations of teicoplanin, there were no symptoms or laboratory abnormalities.

Contact the Poisons Information Centre on 0800 POISON or 0800 764 766 for advice on management of overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Glycopeptide Antibacterials, ATC code: J01XA 02

Teicoplanin is a complex mixture of 6 major components with molecular weights ranging from 1564 - 1894.

Teicoplanin is a glycopeptide antibiotic that has shown in vitro bactericidal activity against both anaerobic and aerobic gram-positive organisms.

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. It is active against staphylococci (including those resistant to methicillin and other beta-lactam antibiotics), streptococci, enterococci, *Listeria monocytogenes*, micrococci, group J/K corynebacteria, and gram-positive anaerobes including *Clostridium difficile*, and peptococci.

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

Mechanism of resistance

One-step resistance to teicoplanin could not be obtained *in vitro* and multi-step resistance was produced *in vitro* only after multiple passages.

There have been reports of elevated MICs for teicoplanin in several strains of *Staphylococcus haemolyticus*, but the clinical relevance is not yet known.

Teicoplanin does not show cross-resistance with other classes of antibiotics. Some cross-resistance has been observed between teicoplanin and the glycopeptide vancomycin among enterococci.

Teicoplanin is taken up by leukocytes and macrophages and retains staphylococcal activity within these cells.

5.2 PHARMACOKINETIC PROPERTIES

Teicoplanin is administered by parenteral injection. The bioavailability of a single 3-6 mg/kg intramuscular injection is over 90%.

Absorption

Following oral administration, teicoplanin is not systemically absorbed from the normal gastrointestinal tract; 40% of the administered dose is present in the faeces in a microbiologically active form.

Distribution

Following intravenous administration of 3-6 mg/kg, the plasma concentration-time profile 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). The elimination half-life is about 150 hours. This long half-life allows once a day administration; but without a loading dose, a steady-state plasma concentration of 14 mg/L would be attained in 2-3 weeks. With a loading dose of 6 mg/kg every twelve hours, a predicted trough plasma

concentration of 10 mg/L, should be attained by the 4th dose. Total plasma clearance is 13.6 mL/h/kg.

The drug distributes readily into skin and blister fluid, myocardium, pulmonary tissue and pleural fluid, bone and synovial fluid but not readily into cerebrospinal (CSF) fluid. It is 90-95% bound with weak affinity to plasma proteins.

Steady-state volume of distribution after 3 - 6 mg/kg IV ranges from 0.94 - 1.4 L/kg.

Biotransformation

Metabolic transformation is minor, about 3%;

Elimination

About 80% of administered drug is excreted in the urine. Renal clearance after 3 - 6 mg/kg IV ranges from 10.4 - 12.1 mL/h/kg

5.3 PRECLINICAL SAFETY DATA

No further relevant information other than that which is included in the other sections of the Data Sheet.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride

Sodium hydroxide (for pH adjustment)

6.2 INCOMPATIBILITIES

Solutions of teicoplanin and aminoglycosides are incompatible and should not be mixed before injection. See section 4.5

This medicine must not be mixed with other medicines except those mentioned in Section 6.6.

6.3 SHELF LIFE

Shelf life of powder as packaged for sale: 3 years

Reconstituted solutions should be stored at 2-8°C (refrigerate, do not freeze) and solutions stored for longer than 24 hours should be discarded. After reconstituting solution **do not store in a syringe**.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25°C.

For storage conditions after reconstitution of the medicine see Section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

Primary Packaging:

Glass vial (Targocid powder for injection)

Glass ampoule (diluent)

Pack sizes:

1 x 400mg powder vial and diluent water for injection

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Preparation of Injection

Note: The powder should be reconstituted strictly in accordance with the instructions below. Errors in reconstitution may result in the formation of a stable foam and delivery of smaller doses.

The entire contents of the accompanying diluent water ampoule should be added **slowly** down the side wall of the vial of Targocid[®]. The vial should be rolled **gently** between the palms until the powder is completely dissolved, taking care to avoid foam formation. **DO NOT SHAKE**. If the solution does become foamy, allow to stand for 15 minutes for the foam to subside. Withdraw the entire contents from the vial **slowly** into a syringe, trying to recover most of the solution by placing the needle in the central part of the stopper.

The final solution is isotonic with plasma and has a pH of 7.2 -7.8.

The reconstituted solution contains:

For the 400 mg vial: 400 mg/3.0 mL of teicoplanin.

The reconstituted solution may be injected directly, or alternatively diluted with any of the following diluents.

- 0.9 % Sodium Chloride solution
- Compound sodium lactate solution
- 5 % glucose solution
- 0.18 % Sodium Chloride and 4 % glucose solution

As a matter of good pharmaceutical practice, solutions for intravenous infusion should be used immediately after admixing.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

sanofi-aventis new zealand limited
Level 8, 56 Cawley Street
Ellerslie
Auckland

Freecall No: 0800 283 684

9 DATE OF FIRST APPROVAL

30 June 1994

10 DATE OF REVISION OF THE TEXT

28 September 2017

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	“Hypersensitivity reactions” sub-heading added. No changes to section text.
4.4	Harmonisation of active ingredient names
4.5	Harmonisation of active ingredient names

Section changed	Summary of new information
4.8	Headings updated and reordered to match System organ class list Deafness and anaphylactic shock added Infusion-related events updated to refer to “red man syndrome” Reporting of suspected adverse reactions subsection added.
5.1	ATC code added
5.3	Section added
6.3	Minor changes to align with registered details
6.4	Minor changes to align with registered details
6.5	Description of product in vial/ampoule added for clarity