

# NEW ZEALAND DATA SHEET

## TEICOPLANIN MYLAN



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### 1. Product Name

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TEICOPLANIN MYLAN, 400 mg, powder for injection.

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### 2. Qualitative and Quantitative Composition

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Each vial contains 400 mg of teicoplanin equivalent to not less than 400,000 IU. When reconstituted with 3.2 mL water for injection, the final concentration corresponds to 134 mg of teicoplanin per mL in a clear or yellowish isotonic solution.

Excipient with known effect: Sodium chloride

Each vial contains 20 mg sodium chloride which equates to approximately 9 mg of sodium.

For the full list of excipients, see section 6.1.

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### 3. Pharmaceutical Form

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Teicoplanin Mylan 400mg powder for injection is a white to off-white lyophilized powder or cake, filled in a 20 mL glass vial closed with bromobutyl rubber stopper and flip-off aluminium seal.

The reconstituted solution is clear and yellowish, isotonic with plasma and has a pH of 7.0 – 8.0 (see section 6.6).

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### 4. Clinical Particulars

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#### 4.1 *Therapeutic indications*

Teicoplanin Mylan 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*

##### **Dose**

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:

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

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

## **Special populations**

### **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 12 mg/kg, intravenously, every 12 hours for 3 doses then a daily maintenance dose of 12 mg/kg.

### **Elderly**

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

### **Renal impairment**

For patients with impaired renal function, reduction of dosage is not required until the fourth day of teicoplanin 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 teicoplanin 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 teicoplanin 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.

### **Paediatric**

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

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

### **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).

### **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).

## **4.3 Contraindications**

Teicoplanin is contraindicated in patients who have exhibited previous hypersensitivity to teicoplanin or to any of the excipients listed in section 6.1.

## **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 (e.g. 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 ethacrynic acid).

### **Loading dose regimen**

Patients should be carefully monitored for adverse reactions when teicoplanin loading doses of 12 mg/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**

### **Pregnancy**

Category B3.

Information about placental transfer of teicoplanin is not known. Teicoplanin should not be used during confirmed or presumed pregnancy unless a physician considers that the potential benefits outweigh any possible risk.

## **Breast-feeding**

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

## **Fertility**

Animal reproduction studies have not shown evidence of impairment of fertility or teratogenic effects.

### **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:

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

**Immune system disorders:** rash, pruritus, fever, bronchospasm, anaphylactic reactions, 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.

**Gastrointestinal disorders:** nausea, vomiting, diarrhoea.

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

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

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

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

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

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

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

Treatment of overdose 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.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

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## 5. Pharmacological Properties

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### 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 4<sup>th</sup> 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.

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## **6. Pharmaceutical Particulars**

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### **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**

Unopened vials: 2 years.

Chemical and physical in-use stability of the reconstituted and diluted solution has been demonstrated for 24 hours at 2 to 8°C stored in the original vial.

From a microbiological point of view, the medicine 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 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

Do not store reconstituted solution in a syringe.

### **6.4 Special precautions for storage**

Unopened vials: 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**

Type I colourless glass vials of 20 mL closed with a dark grey bromobutyl rubber stopper and flip-off aluminium overseal. Pack-size of 1 vial.

Vial stopper is composed entirely of siliconised synthetic bromobutyl rubber and is free from natural rubber and natural rubber latex.

Diluent is not supplied with this product.

### **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.

Reconstitute the powder by **slowly** adding 3.2 mL of water for injection down the side wall of the vial of Teicoplanin Mylan. 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 **3 mL** from the vial **slowly** into a syringe, by placing the needle in the central part of the stopper.

Only clear and yellowish reconstituted solutions should be used. The reconstituted solution contains 400 mg of teicoplanin in 3.0 mL, is isotonic with plasma and has a pH of 7.0 – 8.0.

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

This medicinal product is for single use only.

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

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

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## 7. Medicines Schedule

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Prescription Medicine

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## 8. Sponsor Details

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## 9. Date of First Approval

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20 December 2018

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## 10. Date of Revision of the Text

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9 October 2019

### Summary table of changes

Section	Summary of new information
2	Quantity of sodium chloride detailed
4.4	Added in subheading
4.8	Added in and changed names of subheadings. Added deafness and information on 'red man syndrome'.

5.1	Added Pharmacotherapeutic group
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