

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Targocid 200mg

Teicoplanin 200mg Powder for Injection

Targocid 400mg

Teicoplanin 400mg Powder for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Teicoplanin 200mg

Teicoplanin 400mg

3 PHARMACEUTICAL FORM

Powder for Injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

Targocid may be used for antimicrobial prophylaxis in orthopaedic surgery at risk of Gram-positive infection.

4.2 Posology and method of administration

Administration

The reconstituted Targocid injection may be administered directly either intravenously or intramuscularly. The intravenous injection may be administered either as a bolus or as a 30 minute infusion. Dosage is usually once daily but, in cases of severe infection, a second injection should be administered on the first day in order to reach more rapidly the required serum concentrations.

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. In endocarditis and osteomyelitis, treatment for three weeks or longer is recommended.

Determination of teicoplanin serum concentrations may optimise therapy. In severe infections, trough serum concentrations should not be less than 10mg/l. Peak concentrations measured one hour after a 400mg intravenous dose are usually in the range of 20-50mg/l; peak serum concentrations of up to 250mg/l have been reported after intravenous doses of 25mg/kg. A relationship between serum concentration and toxicity has not been established.

Therapeutic dosage:

Adult or elderly patients with normal renal function

Prophylaxis: 400mg intravenously as a single dose at induction of anaesthesia

Moderate infections: Skin and soft tissue infection, urinary tract infection, lower respiratory tract infection

Loading dose: One single i.v. or i.m. injection of 400mg on the first day

maintenance dose: A single i.v. or i.m. injection of 200mg daily

Severe infections: Joint and bone infection, septicaemia, endocarditis

Loading dose: Three 400mg i.v. injections, administered 12 hours apart

Maintenance dose: A single i.v. or i.m. injection of 400mg daily

1. Standard doses of 200 and 400mg equate respectively to mean doses of 3 and 6mg/kg. In patients weighing more than 85kg it is recommended to adapt the dosage to the weight following the same therapeutic schedule: moderate infection 3mg/kg, severe infection 6mg/kg.

2. In some clinical situations, such as infected, severely burned patients or Staphylococcus aureus endocarditis, unit maintenance doses of up to 12mg/kg have been administered (intravenously).

Children

Teicoplanin can be used to treat Gram-positive infections in children from the age of 2 months. For severe infections and neutropenic patients the recommended dose is 10mg/kg every 12 hours for the first three doses; thereafter a dose of 10mg/kg should be administered by either intravenous or intramuscular injection as a single dose each day.

For moderate infections the recommended dose is 10mg/kg every twelve 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 each day.

The recommended dosage regimen for neonates is a loading dose of 16mg/kg followed by a daily dose of 8mg/kg.

In continuous ambulatory peritoneal dialysis

After a single loading IV dose of 400mg if the patient is febrile, the recommended dosage is 20mg/l per bag in the first week, 20mg/l in alternate bags in the second week and 20mg/l in the overnight dwell bag only during the third week.

Adults and elderly patients with renal insufficiency

For patients with impaired renal function, reduction of dosage is not required until the fourth day of Targocid treatment. Measurement of the serum concentration of teicoplanin may optimise therapy (see section 'Administration').

From the fourth day of treatment

In mild renal insufficiency

Creatinine clearance between 40 and 60ml/min, Targocid dose should be halved, either by administering the initial unit dose every two days, or by administering half of this dose once a day.

In severe renal insufficiency

Creatinine clearance less than 40ml/min and in haemodialysed patients, Targocid dose should be one third of the normal 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 dialysis.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Warnings:

Targocid should be administered with caution in patients known to be hypersensitive to vancomycin since cross hypersensitivity may occur. However, a history of the “Red Man Syndrome” that can occur with vancomycin is not a contra-indication to Targocid.

Thrombocytopenia has been reported with teicoplanin, especially at higher doses than those usually recommended. It is advisable for periodic haematological studies to be performed during treatment. Liver and renal function tests are advised during treatment.

Serial renal and auditory function tests should be undertaken in the following circumstances:

Prolonged treatment in patients with renal insufficiency.

Concurrent and sequential use of other drugs which may have neurotoxic and/or nephrotoxic properties. These include aminoglycosides, colistin, amphotericin B, ciclosporin, cisplatin, furosemide and etacrynic acid.

However, there is no evidence of synergistic toxicity with combinations with Targocid.

Dosage must be adapted in patients with renal impairment (see ‘Dosage’).

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 patients condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

4.5 Interaction with other medicinal products and other forms of interaction

Targocid should be used with care in conjunction with or sequentially with other drugs with known nephrotoxic or ototoxic potential. Of particular concern are streptomycin, neomycin, kanamycin, gentamicin, amikacin, tobramycin, cephaloridine, colistin.

In clinical trials teicoplanin has been administered to many patients already receiving various medications including other antibiotics, antihypertensives, anaesthetic agents, cardiac drugs and antidiabetic agents without evidence of adverse interaction.

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

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 Targocid should not be used during confirmed or presumed pregnancy or during lactation unless a physician considers that the potential benefits outweigh a possible risk. There is no information about the excretion of teicoplanin in milk or placental transfer of the drug.

4.7 Effects on ability to drive and use machines

There is no indication to suggest an effect of teicoplanin on a patient's ability to drive or use machinery.

4.8 Undesirable effects

Targocid is generally well tolerated. Side-effects rarely require cessation of therapy and are generally mild and transient: serious side-effects are rare. The following adverse events have been reported:

Local reactions: erythema, local pain, thrombophlebitis, injection site abscess.

Hypersensitivity: rash, pruritis, fever, bronchospasm, anaphylactic reactions, anaphylactic shock, rigors, urticaria, angioedema, rare reports of exfoliative dermatitis, toxic epidermal necrolysis, rare cases of erythema multiforme including Stevens-Johnson Syndrome. In addition, infusion-related events, such as erythema or flushing of the upper body, 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, thrombocytosis, neutropenia, rare cases of reversible agranulocytosis.

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

Renal function: transient elevations of serum creatinine, renal failure.

Central nervous system: dizziness, headache.

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

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

4.9 Overdose

Teicoplanin is not removed by haemodialysis. Treatment of overdosage should be symptomatic. Several overdoses of 100mg/kg/day have been administered in error to two neutropenic patients aged 4 and 8 years. Despite high plasma concentrations of teicoplanin up to 300mg/ml there were no symptoms or laboratory abnormalities.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Teicoplanin is a bactericidal, 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/l):

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/l):

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°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°C 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" (200mg colour coded yellow, 400mg colour coded green).

Pack size: 1 vial

6.6 Special precautions for disposal

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) and 400mg in 3ml (from the 400mg vial).

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.

7 MARKETING AUTHORISATION HOLDER

Sanofi-aventis
One Onslow Street
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8 MARKETING AUTHORISATION NUMBER(S)

200 mg: PL 04425/0088

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2 August 1989/7 March 2001

10 DATE OF (PARTIAL) REVISION OF THE TEXT

29 November 2006

LEGAL CATEGORY:

POM