PRODUCT INFORMATION
TARGOCID

NAME OF THE MEDICINE

Non-proprietary Name

teicoplanin

DESCRIPTION

Teicoplanin is a glycopeptide-antibiotic produced by *Actinoplanes teichomyceticus*. It is presented as a sterile, pyrogen-free ivory white powder for reconstitution with water for injection. It is freely soluble in water and on reconstitution gives a clear solution.

Microbiology

Teicoplanin is bactericidal or bacteriostatic on growing populations of susceptible Gram-positive organisms; depending on the sensitivity of the organism and antibiotic concentration.

Teicoplanin inhibits the growth of susceptible organisms by interfering with cell-wall biosynthesis at a different site from that affected by β-lactams. Teicoplanin is therefore effective against staphylococci (including those resistant to methicillin and other β-lactam antibiotics) and streptococci.

Some cross-resistance is observed between teicoplanin and the glycopeptide vancomycin.

Teicoplanin has shown no cross-resistance to β-lactam antibiotics, macrolides, aminoglycosides, tetracycline, rifampicin or chloramphenicol.

PHARMACOLOGY

Pharmacokinetics

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 3 hours). At the end of the distribution phase, plasma levels and the subsequent time-concentration curves, are identical following intramuscular or intravenous administration of 3 mg/kg dose. Following intramuscular injection bioavailability is 100%; average peak plasma levels of 7.1 μg/mL are achieved in 3-4 hours following a dose of 3 mg/kg.

The elimination half-life is 70-100 hours. The apparent volume of distribution at steady state is similar to total body water, i.e. 0.6 L/kg.

Approximately 90-95 % of teicoplanin is bound to plasma proteins. Teicoplanin penetrates into blister exudates and bone where it achieves peak concentrations comparable to those in serum after intramuscular injection. Peak levels in joint fluid are approximately 60 % of peak serum concentrations. Teicoplanin penetrates very poorly into cerebrospinal fluid (CSF) and red blood cells.

Metabolic transformation is minor, about 3%; about 80% of administered drug is excreted in the urine over a 16 day collection period.

INDICATIONS

Targocid is indicated for the treatment of the following serious infections due to staphylococci or streptococci, which cannot be treated satisfactorily with less toxic agents, including β-lactam antibiotics:-

Bone - osteomyelitis

Joints - septic arthritis

Blood - non-cardiac bacteraemia, septicaemia

CONTRAINDICATIONS

Targocid is contraindicated in patients with known hypersensitivity to the drug.

PRECAUTIONS

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 contraindication to Targocid.

Periodic haematological studies, and renal and liver function tests are advised during prolonged treatment. Serial renal and auditory function tests should be undertaken in the following circumstances:

- In patients receiving prolonged therapy.
- In patients with renal insufficiency.
- During concurrent and sequential use of other drugs which may have ototoxic or nephrotoxic properties. These include aminoglycosides, amphotericin, cyclosporin, cisplatin, frusemide and ethacrynic acid. However, there are no toxicity data on the concurrent use of these drugs with Targocid.

Superinfection

The use of Targocid may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If new infections due to bacteria or fungi appear during treatment, appropriate measures should be taken.

The safety and efficacy of Targocid by the intrathecal route has not been studied.

Solutions of Targocid and aminoglycosides are incompatible when mixed directly and therefore should not be mixed before injection.

Interactions

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

Use in pregnancy and lactation

(Use in pregnancy category B3)

Reproductive studies in rats and rabbits with subcutaneous doses up to 200 mg/kg/day and 15 mg/kg/day respectively did not reveal teratogenic effects. Teicoplanin was associated with an increase in the number of stillborn pups when rats were treated with subcutaneous doses $\geq$ 100 mg/kg/day. Pup weight was reduced at all doses tested (SC doses $\geq$ 10 mg/kg/day). It is not known if teicoplanin is excreted in breast milk during lactation.

Targocid should not be used during confirmed or presumed pregnancy or during lactation unless the potential benefits outweigh possible risks.

Carcinogenesis and Mutagenesis

Long-term studies in animals to evaluate the carcinogenic potential of teicoplanin have not been performed. Teicoplanin was negative in assays evaluating the potential to cause gene mutations, but assays to evaluate the potential to cause chromosome damage have not been performed.

ADVERSE EFFECTS

In an open clinical trial involving patients with bone or joint infections, teicoplanin was associated with adverse reactions in 32% of the patients. However, treatment was discontinued because of adverse reactions in 17% of patients only. A clear cause-effect relationship was not established in these patients. The most frequent adverse reactions were fever, rashes, nausea, vomiting, rigors, pruritus and diarrhoea.

The following adverse effects have been reported:

- Local reactions: pain, phlebitis, redness, abscess, thrombophlebitis
- Hypersensitivity: skin rash, erythema, pruritus, rigor, fever, bronchospasm, anaphylaxis, urticaria, angioedema, toxic epidermal necrolysis, erythema multiforme including Stevens-Johnson syndrome and rare reports of exfoliative dermatitis
- Hepatic: increased transaminases and/or alkaline phosphatase
- Haematologic: eosinophilia, thrombocytopenia, leucopenia, neutropenia and rare cases of reversible agranulocytosis
- Renal: rise in serum creatinine, blood urea, acute renal failure
- Gastrointestinal: nausea or vomiting, diarrhoea
- Nervous system: dizziness, headache, seizures with intraventricular use
- Auditory: hearing loss, tinnitus, vertigo, other vestibular disorders.

In addition, infusion-related events, such as erythema or flushing of the upper body, have been rarely reported. These events occurred without a history of previous Targocid 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.

DOSAGE AND ADMINISTRATION

Note: Special instructions apply for reconstitution. See below.

The reconstituted Targocid injection should be administered intravenously or intramuscularly. Intravenous dosing may be by slow injection over 5 minutes or by infusion over 30 minutes. Maintenance dosage is once daily; however, initially a loading dose regimen of three doses at 12-hourly intervals is recommended, for rapid attainment of steady-state plasma levels.

An intramuscular injection of Targocid should not exceed 3 mL (400 mg) at a single site.

Adults:

Septicaemia/bacteraemia, acute or chronic osteomyelitis:

Treatment should be started with 400-800 mg (or 6-12 mg/kg) by the I.V. route every 12 hours for 3 doses then the daily maintenance dose should be 400 mg (or 6 mg/kg).

Septic arthritis

Patients with septic arthritis should receive 800 mg (or 12 mg/kg), intravenously, every 12 hours for 3 doses then a daily maintenance dose of 800 mg (or 12 mg/kg).

Elderly Patients:

As for adults. If renal function is impaired, the instructions for impaired renal function should be followed.

While the total duration of therapy is determined by the type and severity of infection and by the clinical response of the patient, the following periods are often appropriate:

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

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 15μg/mL in other cases.

From the fourth day of treatment:

in mild renal insufficiency:

creatinine clearance between 40 and 60 mL/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 40 mL/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.**

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.

Satisfactory potency of the reconstituted injection is retained for 48 hours at 25oC and for 7 days at 4°C. As a matter of good pharmaceutical practice, it is recommended that reconstituted solutions be stored under refrigeration (4oC) and solutions stored longer than 24 hours be discarded. When storing reconstituted solution **do not store in a syringe.**

The reconstituted solution contains:

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

Dilution of reconstituted solution:

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

If necessary, solutions with the above diluents may be stored at 4°C for up to 7 days. Solutions left at room temperature for longer than 24 hours should be discarded.

- 5% glucose solution
- 0.18% Sodium Chloride and 4% glucose solution

Solutions containing the above diluents (which contain glucose) should be stored at 4°C and should be used within 24 hours; solutions kept longer than 24 hours should be discarded.

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

OVERDOSAGE

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

PRESENTATION

Targocid 400 mg - 25 mL vial containing lyophilised 460 mg* teicoplanin and 24.8 mg sodium chloride with an accompanying ampoule (3.14 mL*) Water for Injections (Ph. Eur.)

* An overage is included to allow withdrawal of the correct dose.

NAME AND ADDRESS OF SPONSOR

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