TEICOPLANIN

BRUTIO 200

℞

200 mg Lyophilized Powder for Injection (I.M./I.V.)
ANTIBACTERIAL (GLYCOPEPTIDE)

FORMULATION:
Each vial contains:
Teicoplanin, BP..... 200 mg

PRODUCT DESCRIPTION:
Off white to yellowish lyophilized mass filled in clear glass tubular vials.
Teicoplanin belongs to a group of antibiotics called glycopeptides. Bacteria have an external cell wall that is reinforced by molecules called peptidoglycans. The cell wall is vital for protection against the normal environment of the body in which the bacteria live. Teicoplanin works by blocking the formation of these peptidoglycans. By doing this the walls of the bacteria become weak and this results in the death of the bacteria. Teicoplanin is used to treat serious infections of the heart and blood. It is not absorbed from the gut and is therefore only given by injection or infusion.

PHARMACOLOGICAL ACTION:
Lyophilized teicoplanin is a bactericidal glycopeptide antibiotic produced by fermentation of *Aclinoplanes teicomyceticus*. It is active *in vitro* against both aerobic and anaerobic Gram-positive bacteria.
Species usually sensitive: *Staphylococcus aureus*, 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:
Nocardia asteroides, lactobacillus spp., Leuconostoc and all Gram-negative bacteria. Bactericidal synergy has been demonstrated *in vitro*, in combination with aminoglycosides, against group 0 *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 resistancewas only reached *in vitro* after 11 to 14 passages.
Teicoplanin does not show cross-resistance with other classes of antibiotics. Following intravenous and intramuscular administration, Teicoplanin is widely distributed in body tissues. It is slowly eliminated with a plasma half-life of 70 to 100 hours; the excretory route is renal. Teicoplanin is not absorbed when administered orally. Teicoplanin does not penetrate through the blood-brain barrier.

PHARMACOKINETICS PROPERTIES:
Absorption:
Teicoplanin is administered by parenteral route (intravenously or intramuscularly). After intramuscular administration, the bioavailability of Teicoplanin (as compared to intravenous administration) is almost complete (90%). After six daily intramuscular administrations of 200 mg the mean (SD) maximum Teicoplanin concentration (Cmax) amounts to 12.1 (0.9) mg/L and occurs at 2 hours after administration.
After a loading dose of 6 mg/kg administered intravenously every 12 hours for 3 to 5 administrations, Cmax values range from 60 to 70 mg/L and Ctrough are usually above 10 mg/L. After an intravenous loading dose of 12 mg/kg administered every 12 hours for 3 administrations, mean values of Cmax and Ctrough are estimated to be around 100 mg/L and 20 mg/L, respectively.
After a maintenance dose of 6 mg/kg administered once daily Cmax and Ctrough values are approximately 70 mg/L and 15 mg/L, respectively.
After a maintenance dose of 12 mg/kg once daily Ctrough values range from 18 to 30 mg/L.
When administered by oral route Teicoplanin is not absorbed from the gastrointestinal tract. When administered by oral route at 250 or 500 mg single dose to healthy subjects, Teicoplanin is not detected in serum or urine but only recovered in feces (about 45% of the administered dose) as unchanged medicinal product.
Distribution
The binding to human serum proteins ranges from 87.6 to 90.8% without any variation in function of the teicoplanin concentrations. Teicoplanin is mainly bound to human serum albumin. Teicoplanin is not distributed in red cells.
The volume of distribution at steady-state (Vss) varies from 0.7 to 1.4 L/kg. The highest values of Vss are observed in the recent studies where the sampling period was superior to 8 days.
Teicoplanin distributed mainly in lung, myocardium and bone tissues with tissue/serum ratios superior to 1. In blister fluids, synovial fluid and peritoneal fluid the tissue/serum ratios ranged from 0.5 to 1. Elimination of Teicoplanin from peritoneal fluid occurs at the same rate as from serum. In pleural fluid and subcutaneous fat tissue the tissue/serum ratios are comprised between 0.2 and 0.5. Teicoplanin does not readily penetrate into the cerebrospinal fluid (CSF).
Biotransformation
Unchanged form of Teicoplanin is the main compound identified in plasma and urine, indicating minimal metabolism. Two metabolites are formed probably by hydroxylation and represents 2 to 3% of the administered dose.
Elimination
Unchanged teicoplanin is mainly excreted by urinary route (80% within 16 days) while 2.7% of the administered dose is recovered in feces (via bile excretion) within 8 days following administration.
Elimination half-life of Teicoplanin varies from 100 to 170 hours in the most recent studies where blood sampling duration is about 8 to 35 days.
Teicoplanin has a low total clearance in the range of 10 to 14 mL/h/kg and a renal clearance in the range of 8 to 12 mL/h/kg indicating that Teicoplanin is mainly excreted by renal mechanisms.
Linearity
Teicoplanin exhibited linear pharmacokinetics at dose range of 2 to 25 mg/kg.
Special populations
• Renal impairment:
As Teicoplanin is eliminated by renal route, Teicoplanin elimination decreases according to the degree of renal impairment. The total and renal clearances of Teicoplanin depends on the creatinine clearance.
• Elderly patients:
In the elderly population the Teicoplanin pharmacokinetics is not modified unless in case of renal impairment.
• Paediatric population
A higher total clearance (15.8 mL/h/kg for neonates, 14.8 mL/h/kg for a mean age 8 years) and a shorter elimination half-life (40 hours neonates; 58 hours for 8 years) are observed compared to adult patients.

INDICATIONS:
Teicoplanin is indicated in potentially serious Gram-positive infections, including those which cannot be treated with other antimicrobial drugs. The effectiveness of Teicoplanin has been documented in the following infections caused by organisms sensitive to Teicoplanin: endocarditis. septicaemia and osteomyelitis, respiratory infections, skin and soft tissue infections, urinary tract infections and peritonitis associated with chronic ambulatory peritoneal dialysis (CAPD).

DOSAGE AND ADMINISTRATION:
The reconstituted Teicoplanin injection may be administered 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 the required serum concentrations more rapidly.
The majority of patients, with infections caused by organisms sensitive to the antibiotic, show a therapeutic response within 48 to 72 hours. The 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.
Loading Dose: 400 mg I.V. injections administered 12 hours apart.
Maintenance dose: A single I.V. or I.M. injection of 400 mg daily.

THERAPEUTIC DOSAGE:
Adults and elderly patients with normal renal function:
Moderate infections: Skin and soft tissue infections, urinary tract infections, lower respiratory tract infections,
Loading dose: One single I.V. injection of 400 mg (two vials) on the first day.
Maintenance dose: A single I.V. or I.M. injection of 200 mg daily.
Severe infections: Joint and bone infections, septicaemia, endocarditis.
Loading dose: 400 mg I.V., injection every 12 hours for the first three doses.
Maintenance dose: A single I.V., or I.M. injection of 400 mg daily.
In some clinical situations, such as infected, severely bowled patients or Staphylococcus aureus endocarditis, unit maintenance doses of up to 12 mg per kg maybe required.
Note: Standard doses of 200 and 400 mg are equivalent to mean doses of 3 mg per kg and 6 mg per kg respectively. In overweight patients it is recommended that the dose be adapted 10 the weight of the patient as follows: moderate infections 3 mg per kg; severe infections 6 mg per kg.
Children: Teicoplanin can be used to treat Gram positive infections in children from the age of three years.
For severe infections and neutropenic patients the recommended dose is 10 mg per kg every 12 hours, by intravenous injection, for the first three doses. Thereafter a dose of 10 mg per kg should be administered by either intravenous or intramuscular injection as a single dose each day. For moderate infections the recommended dose is 10 mg per kg by intravenous injection, every twelve hours for thefirst three doses.
Thereafter a dose of 6 mg per kg should be administered by intravenous or intramuscular injection as a single dose each day.

DIRECTIONS FOR RECONSTITUTION:
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. 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 25°C and for 7 days at 4°C. As a matter of good pharmaceutical practice, it is recommended that reconstituted solutions be stored under refrigeration (4°C) and solutions stored longer than 24 hours be discarded. When storing reconstituted solution do not store in a syringe.

CONTRAINDICATIONS:
Hypersensitivity to Teicoplanin.
Safety and efficacy has not been established in children under three years of age.
Teicoplanin should not be used during pregnancy and lactation, as safety has not been established. It is not known whether Teicoplanin passes into breast milk.
Teicoplanin should not be injected into the subarachnoid space.

WARNINGS:
Teicoplanin should be administered with caution in patients known to be hypersensitive to vancomycin since cross hypersensitivity may occur. However a history of "Red Man Syndrome" that can occur with vancomycin, is not a contraindication to Teicoplanin. Thrombocytopenia has been reported with Teicoplanin especially at doses higher than those usually recommended. It is advisable for periodic haematological studies to be performed during treatment. Liver and renal function tests are recommended during treatment. Serial renal and auditory function tests should be undertaken in the following circumstances: Prolonged treatment in patients with renal insufficiency.

DRUG INTERACTIONS:
Concurrent and sequential use of other drugs which may have neurotoxic and nephrotoxic properties.
These include aminoglycosides, colistin, amphotericin B, cyclosporin, cisplatin, furosemide and ethacrynic acid. However, there is no evidence of synergistic toxicity when Teicoplanin is used in combination with the above drugs.

FERTILITY, PREGNANCY AND LACTATION:
Pregnancy:
There are a limited amount of data from the use of teicoplanin in pregnant women. Studies in animals have shown reproductive toxicity at high doses in rats there was an increased incidence of stillbirths and neonatal mortality. The potential risk for humans is unknown.
Therefore, Teicoplanin should not be used during pregnancy unless clearly necessary. A potential risk of inner ear and renal damage to the fetus cannot be excluded.
Breastfeeding:
It is unknown whether Teicoplanin is excreted in human milk. There is no information on the excretion of Teicoplanin in animal milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with Teicoplanin should be made taking into account the benefit of breast-feeding to the child and the benefit of Teicoplanin therapy to the mother.
Fertility:
Animal reproduction studies have not shown evidence of impairment of fertility.

ADVERSE DRUG REACTIONS:
The following side-effects have been reported. In clinical studies: occasional hypersensitivity reactions, exanthema, erythema, pruritus, fever, bronchospasm and anaphylactic reactions. Pain at the injection site and phlebitis or the formation of an abscesshave been observed occasionally.
In some cases a rise in the transaminase and/or alkaline phosphatase has been observed. A rise in serum creatinine may also occur.
Eosinophilia, thrombocytopenia or leucopenia have been described.
Teicoplanin can, on rare occasions, lead to nausea and vomiting, headache or dizziness.
Loss of hearing, tinnitus or vestibular disturbances have been observed in patients treated with in combination with a potentially ototoxic Teicoplanin drug such as an aminoglycoside.
Local reactions: erythema, thrombophlebitis
Allergic: rash, pruritus, severe bronchospasm, anaphylactic reactions
Gastrointestinal; nausea, vomiting, diarrhoea
Blood: eosinophilia, leucopenia, neutropenia, thrombocytopenia, thrombocytosis
Liver function: increases in serum transaminases and/or serum alkaline phosphatase
Renal function: transient elevations of serum creatinine
Central nervous system: dizziness and headache.

OVERDOSE AND TREATMENT:
Symptomatic measures are recommended for the management of an overdose. Available information on two children with agranulocytosis to whom several doses of 100 mg per kg per day were administered in error, shows that despite very high serum concentrations of 300 mg per litre, no intoxication phenomena appeared.
Teicoplanin is not removed by haemodialysis or peritoneal dialysis.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

KEEP ALL MEDICINES OUT OF CHILDREN'S REACH.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

AVAILABILITY:
USP Type I Clear Glass Vial with Yellow Flip-Off Seal (Box of 1's).

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