Approved Package Insert

SCHEDULING STATUS

TEGORID IV 200 & TEGORID IV 400 S4

PROPRIETARY NAME and dosage form

TEGORID IV 200 & TEGORID IV 400 Freeze-dried powder for injection

COMPOSITION

TEGORID IV 200

Per vial: Lyophilised teicoplanin 200 mg.

TEGORID IV 400

Per vial: Lyophilised teicoplanin 400 mg.

Excipients: **TEGORID IV 200** and **TEGORID IV 400** also contain sodium chloride.

Reconstitute before use.

PHARMACOLOGICAL CLASSIFICATION

A 20.1.1 Broad and medium spectrum antibiotics

PHARMACOLOGICAL ACTION

Pharmacodynamics

Teicoplanin is a bactericidal, glycopeptide antibiotic, produced by fermentation of *Actinoplanes teicomyceticus*. It is active *in vitro* against both aerobic and anaerobic Gram-positive bacteria.

Bactericidal synergy has been demonstrated, *in vitro,* in combination 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 to 14 passages. Teicoplanin does not show cross-resistance with other classes of antibiotics.

Species usually sensitive:

Staphyllococcus aureus and coagulase negative staphylococci (sensitive or resistant to meticillin), streptococci, enterococci, *Listeria monocytogenes,* micrococci, group JK Corynebacteria, Gram-positive anaerobes including *Clostridium difficile* and peptococci.

In vitro sensitivity does not necessarily imply clinical efficacy.

Species usually resistant:

Nocardia asteroides, Lactobacillus spp., Leuconostoc and all Gram-negative bacteria.

Pharmacokinetics

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.

INDICATIONS

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

TEGORID IV may be used as prophylaxis in orthopaedic and vascular surgery at risk of Gram-positive infection.

CONTRA-INDICATIONS

Hypersensitivity to teicoplanin or any of the ingredients of **TEGORID IV**.

Children under three years of age, as safety and efficacy have not been established in this age group.

Pregnancy and lactation (see PREGNANCY AND LACTATION).

TEGORID IV must not be injected into the subarachnoid space.

WARNINGS

TEGORID IV 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' which can occur with vancomycin, is not a contra-indication to **TEGORID IV**. Thrombocytopenia has been reported with **TEGORID IV**, 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.
- concurrent and sequential use of other agents which may have neurotoxic and/or nephrotoxic properties. These include aminoglycosides, colistin, amphotericin B, ciclosporin, cisplatin, furosemide and ethacrynic acid.

However, there is no evidence of synergistic toxicity when **TEGORID IV** is used in combination with the above medicines.

INTERACTIONS

TEGORID IV should be used with care in conjunction with or sequentially with other medicines with known nephrotoxic or ototoxic potential. Of particular concern are

streptomycin, neomycin, kanamycin, gentamycin, amikacin, tobramycin, cephalorodine and colistin.

PREGNANCY AND LACTATION

TEGORID IV should not be used during pregnancy and lactation, as safety has not been established. It is not known whether **TEGORID IV** passes into breast milk (see **CONTRA-INDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE

The reconstituted **TEGORID IV** injection may be administered either intravenously or intramuscularly. The intravenous injection may be administered either as a bolus or as a 30 minute infusion.

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.

Determination of teicoplanin serum concentrations may optimise therapy. In severe infections, trough serum concentrations should not be less than 10 mg per litre. Peak concentrations measured one hour after a 400 mg intravenous dose are usually in the range of 20 to 50 mg per litre; peak serum concentrations of up to 250 mg per litre have been reported after intravenous doses of 25 mg per kg.

A relationship between serum concentration and toxicity has not been established.

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:

A single IV injection of 400 mg on the first day.

Maintenance dose:

A single IV or IM injection of 200 mg daily.

Severe infections:

Joint and bone infections, septicaemia, endocarditis.

Loading dose:

400 mg IV injection every 12 hours for the first three doses.

Maintenance dose:

A single IV or IM injection of 400 mg daily.

In some clinical situations, such as infected, severely burned patients or *Staphyllococcus aureus* endocarditis, unit maintenance doses of up to 12 mg per kg may be required.

Note:

Standard doses of 200 mg 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 to the weight of the patient as follows: moderate infections 3 mg per kg; severe infections 6 mg per kg.

PROPHYLAXIS IN ORTHOPAEDIC AND VASCULAR SURGERY AT RISK OF GRAM-POSITIVE INFECTION:

400 mg intravenously as a single dose at induction of anaesthesia.

CHILDREN:

TEGORID IV 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 the first three doses. Thereafter a dose of 6 mg

per kg should be administered by either intravenous or intramuscular injection as a single dose each day.

ADULTS AND ELDERLY PATIENTS WITH RENAL INSUFFICIENCY:

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

From the fourth day of treatment:

In mild renal insufficiency:

Creatinine clearance between 40 ml and 60 ml per minute: the dose of **TEGORID IV** should be halved either by administering the initial unit dose every two days, or by administering half the initial unit dose once a day.

In severe renal insufficiency:

Creatinine clearance less than 40 ml per minute and in haemodialysed patients: the dose of **TEGORID IV** should be one third of the normal dose either by administering the initial unit dose every third day, or by administering one third of the unit dose once a day. **TEGORID IV** is not removed by dialysis.

Unless measurement of the serum concentrations can be guaranteed to accompany the therapy, patients with a creatinine clearance lower than or equal to 20 ml per minute must be excluded from therapy with **TEGORID IV**.

In continuous ambulatory peritoneal dialysis:

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

TEGORID IV is stable in peritoneal dialysis solutions (1,36 % or 3,86 % dextrose).

Do not keep mixed solutions for more than 24 hours.

MONITORING THE PLASMA CONCENTRATIONS:

If checks are carried out on the teicoplanin serum level in patients with severe infections, then the minimum serum level should not be below 10 mg per litre (measured just before the following dose).

TYPE OF ADMINISTRATION AND DURATION OF USE:

1. Type of administration:

In order to produce the ready-to-use solution, 3 mL of water for injection is injected slowly into the vial with the dry substance. The vial is then rolled gently between the palms until the dry substance is completely dissolved. To avoid the formation of foam, **do not shake the vial.** If foam does develop during the preparation of the injection solution, it is recommended that the solution be left to stand for approximately 15 minutes until the foam has disappeared. **TEGORID IV** may be administered by either intravenous or intramuscular injection. The intravenous dose may be given by rapid injection over one minute or by short infusion.

Following preparation of the ready-to-use solution, **TEGORID IV** is injected directly intravenously or into the proximal end of a drip line after clamping the line. **TEGORID IV** can be injected quickly, i.e. within one minute. **TEGORID IV** can also be injected intramuscularly.

For the purposes of infusion, **TEGORID IV** is dissolved in 20 to 50 ml of infusion solution and administered over 20 to 30 minutes.

The following infusion solutions are suitable for mixing with **TEGORID IV**.

- Isotonic saline solution 0,95 %
- Ringer’s solution
- Ringer’s lactate solution
- 5 % glucose solution
- Solutions containing 0,18 % sodium chloride and 4 % glucose

Reconstituted solutions of **TEGORID IV** should be used as soon as possible otherwise they may be stored for 24 hours at 2 to 8 ºC.

TEGORID IV and aminoglycosides are incompatible and should not be mixed in the same solution.

2. Duration of use:

With infections caused by teicoplanin-sensitive pathogens, a therapeutic result is shown in the majority of cases within 48 to 72 hours.

The duration of treatment is based upon the severity of the infection as well as upon the clinical and bacteriological progress. The treatment should be continued for at least three days after the patient has become afrebile and after the disappearance of clinical symptoms.

In cases of endocarditis or osteomyelitis, at least three weeks treatment is recommended.

TEGORID IV should not be administered for longer than four months.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects

The following side-effects have been observed:

Infections and infestations

Frequency unknown: Superinfections (overgrowth of non-susceptible organisms).

Blood and the lymphatic system disorders

Less frequent: Eosinophilia, thrombocytopenia, leucopenia.

Frequency unknown: Agranulocytosis, neutropenia.

Immune system disorders

Less frequent: Hypersensitivity reaction, exanthema, erythema, pruritus, fever, bronchospasm, angioedema, anaphylactic reactions and anaphylactic shock.

Nervous system disorders

Less frequent: Headache, dizziness.

Frequency unknown: Seizures with intraventricular use.

Ear and labyrinth disorders

Frequency unknown: Loss of hearing, tinnitus or vestibular disturbances.

Vascular disorders

Less frequent: Phlebitis.

Frequency unknown: Thrombophlebitis.

Gastro-intestinal disorders

Less frequent: Nausea, vomiting, diarrhoea.

Respiratory, thoracic and mediastinal disorders

Less frequent: Bronchospasm.

Skin and subcutaneous tissue disorders

Frequent: Erythema, rash, pruritus.

Frequency unknown: Urticaria, exanthema, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome.

Renal and urinary disorders

Frequency unknown: Renal failure.

General disorders and administration site conditions

Less frequent: Pain at the injection site and phlebitis, the formation of an abscess.

Investigations

Frequency unknown: A rise in the transaminase and/or alkaline phosphatase, a rise in serum creatinine.

Special Precautions

In patients with restricted kidney function, the therapy should be monitored carefully. Where treatment in such patients is continued for longer than three weeks, regular checks are recommended on the serum level as well as on kidney, liver and auditory functions.

Such tests are also recommended in cases of concurrent and sequential use of other agents which may have neurotoxic and/or nephrotoxic properties e.g. aminoglycosides, colistin, amphotericin, ciclosporin, cisplatin, furosemide and ethacrynic acid.

Unless measurement of the serum concentrations can be guaranteed to accompany the therapy, patients with a creatinine clearance lower than or equal to 20 ml per minute must be excluded from therapy with **TEGORID IV**. **TEGORID IV** may not be administered into the subarachnoid space.

Periodic haematological studies plus liver and renal function tests are advisable during prolonged treatment. Administer with caution to patients known to be vancomycin-sensitive since cross-hypersensitivity may occur.

Superinfection: The use of **TEGORID IV**, 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.

Effects on ability to drive and use machines:

When driving vehicles or operating machinery it must be borne in mind that dizziness has been reported during treatment with **TEGORID IV**.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Generally symptomatic measures are recommended for the management of an overdose.

TEGORID IV is not removed by haemodialysis or peritoneal dialysis.

IDENTIFICATION

Vial: White or slightly brown lyophilised powder.

TEGORID IV is packed in a 10 ml type II clear glass vial with a grey chlorobutyl rubber stopper and aluminium flip-off cap with a blue (for the **TEGORID IV 200**) and a green (for the **TEGORID IV 400**) polypropylene cover.

Reconstituted solution: Clear, transparent and slightly brown solution.

PRESENTATION

TEGORID IV 200:

Pack of 1 x 10 ml clear glass vial containing 200 mg of lyophilised teicoplanin substance.

TEGORID IV 400:

Pack of 1 x 10 ml clear glass vial containing 400 mg of lyophilised teicoplanin substance.

STORAGE INSTRUCTIONS

Lyophilised powder: Store at or below 25 °C and protect from moisture. Do not remove from the carton until required for use.

Reconstituted solution: Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8 ºC. From a microbiological point of view, the product 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 ºC, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Protect from freezing.

This product is for single use only. Any unused portion should be discarded in accordance with local requirements.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

TEGORID IV 200: 45/20.1.1/0100

TEGORID IV 400: 45/20.1.1/0101

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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