SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

TEİKOPOL 200 mg Powder and Solvent for Solution for I.M./I.V. Injection

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
A vial contains 200 mg of Teicoplanin

Excipients:
Sodium chloride 24.0 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilized powder for solution for injection
The appearance of the reconstituted solution is in the form of a clear, yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TEİKOPOL is indicated for the treatment of infections caused by sensitive gram-positive bacteria, including those resistant to other antibiotics (such as methicillin and cephalosporins): endocarditis, septicemia, bone and joint infections, respiratory tract infections, skin and soft tissue infections, urinary tract infections and peritonitis associated with chronic ambulatory peritoneal dialysis.

TEİKOPOL is also indicated for the treatment of infections in patients allergic to penicillin or cephalosporins.

TEİKOPOL can be used for prophylaxis in patients in whom infections due to gram-positive bacteria constitute a risk (for example, patients requiring dental or orthopedic surgery).

TEİKOPOL can be used orally in the treatment of antibiotic-related diarrhea caused by *Clostridium difficile*.

4.2 Posology and method of administration

Posology/frequency and duration of administration

Adults or elderly patients with normal renal function

Prophylaxis: During anesthesia induction administered intravenously as a single dose 400 mg.

In moderate infections: Skin and soft tissue infection, urinary infection, lower respiratory tract infection.
Loading dose: First day via I.M. or I.V. as a single dose 400 mg.
Maintenance dose: Via I.M or I.V. as a single dose 200 mg per day.

In severe infections: joint and bone infection, septicemia, endocarditis.
Loading dose: Administered via I.V. three times as 400 mg with 12 hours intervals.
Maintenance dose: Via I.M or I.V. as a single dose 400 mg per day.

1. Standard doses of 200 and 400 mg are equivalent to doses of 3 and 6 mg/kg, respectively. In patients with a body weight greater than 85 kg, it is recommended that the dosage is adjusted according to the body weight with respect to the same treatment scheme: 3 mg/kg in moderate intensity infections and 6 mg/kg in severe infections.

2. In some clinical conditions, such as infected, severe burns or *Staphylococcus aureus* endocarditis, maintenance doses up to 12 mg/kg are administered (intravenously). In the endocarditis where *Staphylococcus aureus* is a causative agent, satisfactory results have been obtained with teicoplanin which is applied in the form of polytherapy. When serum concentrations are controlled for severe infections, valley values should be 10 times higher than MIC value or 10 mg/l in general.

Diarrhea associated with antibiotics caused by Clostridium difficile:
Oral doses of 200 mg twice per day.

Combined treatment:
When the infection requires maximum antibacterial activity (i.e. in staphylococcal endocarditis) and the presence of mixed infection with gram negative agents cannot be eliminated (i.e. in the empirical treatment of fever in a neutropenic patient), it is recommended to combine treatment with an appropriate antibacterial agent.

Endocarditis prophylaxis with gram-positive bacteria in dental surgery and patients with heart valve disease:
During induction of anesthesia 400 mg (6 mg / kg) I.V. teicoplanin.

Method of administration:

The reconstituted TEİKOPOL injection may be administered directly by intravenously or intramuscularly. Intravenous doses may be administered as bolus (by rapid injection in 3-5 minutes) or by slow infusion in 30 minutes. Only infusion technique should be used in neonates.

Dosage is usually in the form of a single dose per day, but in severe infections, a second injection may be administered on the first day to achieve the desired serum concentrations more quickly.

Intraventricular administration of teicoplanin is not indicated (see Sections 4.4 and 4.8).

In infections where antibiotic sensitive organisms are involved, most patients respond to treatment within 48-72 hours. The total duration of treatment 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.

TEİKOPOL should not be applied for more than 4 months.

Detection of serum concentrations of teicoplanin may optimize treatment. In severe infections, serum valley concentrations should not be less than 10 mg/l. The peak concentrations measured one hour after administration of an intravenous dose of 400 mg are usually in the range 20-50 mg/l; Following administration of 25 mg/kg intravenous doses, peak serum concentrations up to 250 mg/l were reported. No relationship between serum concentrations and toxicity was detected.

Additional information on special populations:

Renal/Hepatic failure:
Dose adjustment is not required until the fourth day of TEİKOPOL treatment, and a dose adjustment should be made so that a serum trough concentration of at least 10 mg/l is obtained.

After the 4th day of treatment:

- In moderate renal failure (creatinine clearance within 40 to 60 ml/min): the recommended normal dose once in 2 days or half of this dose is administered once a day.
- In severe renal insufficiency (creatinine clearance below 40 ml/min) and in patients undergoing hemodialysis: the recommended normal dose should be administered as once in 3 days or one third of this dose per day, and maintenance dose should be reduced to one third of the recommended dose per day.

TEİKOPOL cannot be removed by hemodialysis.
For peritonitis in patients undergoing continuous ambulatory peritoneal dialysis:
After a single loading dose of 400 mg administered intravenously, 20 mg/l in each bag for the first week, a 20 mg/l in two bags for the second week and 20 mg/l for the remaining bag in the third week to be administered overnight. In patients with fever a 400 mg the teicoplanin loading dose should also be applied.

Teicoplanin remains stable in peritoneal dialysis solutions (1.36% or 3.86% dextrose). These solutions should not be stored for longer than 24 hours.

Pediatric population:
For children older than 2 months and under 16 years of age: The recommended dose for most gram-positive infections is the administration of 10 mg/kg intravenous dose every 12 hours for

the first three treatments. The administration is then continued intravenously or intramuscularly at a single dose of 6 mg/kg per day.

In severe infections and infections in neutropenic patients: It is recommended to administer a dose of 10 mg/kg intravenously with 12 hours intervals.

For infants younger than 2 months: The recommended dosage is a single loading dose of 16 mg/kg for the first day of treatment. In the following days, 8 mg/kg once a day as maintenance dose is administered. Doses should be administered by intravenous infusion within 30 minutes.

4.3 Contraindications

TEİKOPOL is contraindicated in patients who have previously been hypersensitive to teicoplanin or any substances in TEİKOPOL.

4.4 Special warnings and precautions for use

Patients who are known to be hypersensitive to vancomycin should not be given TEİKOPOL since cross-sensitivity may be seen. However, the previously described 'Red Man Syndrome' caused by vancomycin; is not a contraindication of teicoplanin use.

Thrombocytopenia has been reported with teicoplanin, especially at higher doses than usually recommended doses. Periodic hematological examinations are recommended during treatment. Liver and kidney function tests are recommended during treatment.
Regular renal and hearing function tests should be performed in the following cases:

- Long-term treatment in patients with renal failure
- In combination with some drugs with neurotoxic and/or nephrotoxic and/or ototoxic properties. Aminoglycoside, colistin, amphotericin B, cyclosporine, cisplatin, furosemide and ethacrynic acid are among these drugs. However, it has not been shown that combinations with teicoplanin show synergistic toxicity.

In patients with renal impairment, the dosage must be adjusted (see section 4.2).

Superinfection: As with other antibiotics, the use of TEİKOPOL especially if prolonged, may result in over-reproduction of non-susceptible microorganisms. The condition of the patient should be re-evaluated. If superinfection develops during treatment, appropriate precautions should be taken.

In some cases of intraventricular use, seizures have been reported.

This medicinal product contains less than 1 mmol (23 mg) of sodium per ml; in other words, "it does not contain sodium".

IT IS ABSOLUTELY USED UNDER THE DOCTOR CONTROL.

4.5 Interaction with other medicinal products and other forms of interaction

TEİKOPOL should be administered with caution when it is used together or consecutively with other drugs known to have nephrotoxic or ototoxic potential, such as aminoglycosides, amphotericin B, cyclosporine and furosemide (see Section 4.4). Streptomycin, neomycin, kanamycin, gentamicin, amikacin, tobramycin, cephaloridine, colistin are drugs that need special attention.

In clinical trials, teicoplanin has been administered to a large number of patients treated with other drugs such as other antibiotics, antihypertensives, anesthetic agents, cardiac drugs and antidiabetic agents, and no adverse interactions have been observed.

Animal studies have shown no interaction with diazepam, thiopental, morphine, neuromuscular blockers or halothane.

4.6 Pregnancy and lactation

General recommendation
Pregnancy category: C

Women with childbearing potential/Contraception
There is no information on the use of teicoplanin in women with childbearing potential. Therefore, teicoplanin should not be used in women with childbearing potential unless explicitly necessary.

Pregnancy
There are limited data on the use of teicoplanin in pregnant women. Animal studies have shown that high doses of reproductive toxicity are present (see section 5.3): In rats there is an increase in neonatal mortality and low incidence in high doses. The potential risk for humans is unknown. Therefore, teicoplanin should not be used during pregnancy unless clearly required. Renal injury and potential risk in the inner ear cannot be underestimated. (see Section 4.4)

Lactation
It is not known whether TEİKOPOL has been excreted with breast milk. There is no information whether teicoplanin is excreted in animals' milk. A decision on whether to continue/discontinue breast-feeding 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.

4.7 Effects on ability to drive and use machines

Teicoplanin can cause dizziness and headache. The ability to drive or use machines may be affected. Patients experiencing these undesirable effects should not drive or use machines.

4.8 Undesirable effects

Reported adverse reactions are indicated below.

Very common (≥ 1/10); common (≥ 1/100 to <1/10); non-widespread (≥ 1 / 1,000 to <1/100); infrequently (≥ 1 / 10,000 to <1 / 1,000); very rare (<1 / 10,000), unknown (cannot be estimated from the available data).

Infections and infestations:

Rare: Abscess

Unknown: Abscess at injection site, superinfection (overproduction of non-sensitive microorganisms)

Diseases of the blood and lymph system:

Uncommon: Eosinophilia, thrombocytopenia, leukopenia

Unknown: Agranulocytosis, neutropenia,

Immune system diseases:

Uncommon: Anaphylactic reactions (anaphylaxis)

Unknown: Anaphylactic shock

Diseases of the nervous system:

Uncommon: dizziness, headache

Unknown: Seizures by intraventricular application.

Ear and inner ear diseases:

Uncommon: deafness (moderate hearing loss), tinnitus and vestibular disorder.

Vascular diseases:

Uncommon: Phlebitis

Unknown: Thrombophlebitis

Respiratory, thoracic and mediastinal disorders:

Uncommon: Bronchospasm

Gastrointestinal diseases:

Uncommon: Nausea, diarrhea, vomiting

Skin and subcutaneous tissue diseases:

Common: Erythema, rash, itching

Unknown: Urticaria, angioedema, exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome

Renal and Urinary disorders:
Unknown: renal failure.

General disorders and administration site conditions:
Common: Pain, Fever
Unknown: Titration

Laboratory investigations:
Uncommon: Abnormal transaminases, abnormal blood alkaline phosphatase, increased blood creatinine

4.9 Overdose and therapy
Cases of accidental administration of excessive doses to pediatric patients have been reported. In one case agitation occurred in a 29-day-old newborn who had been administered 400 mg intravenously (95 mg/kg).

Treatment: Treatment of teicoplanin overdose should be symptomatic. TEİKOPOL cannot be removed by hemodialysis and only slowly by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Glycopeptide Antibacterial
ATC Code: J01XA02

Teicoplanin is a glycopeptide antibiotic with bactericidal effect which is produced by the fermentation of *Actinoplanes teichomyceticus*. It is effective on both aerobic and anaerobic gram-positive microorganisms.

Typically susceptible strains (MIK ≤16 mg/1):
Staphylococcus aureus and (methicillin-sensitive or resistant) coagulase-negative staphylococci, streptococci, enterococci, *Listeria monocytogenes*, micrococci, J/K group corinebacteria, and gram-positive anaerobes including *Clostridium difficile* and peptococci.

Typically, resistant strains (MIK> 16 mg/l):
Nocardia asteroides, Lactobacillus spp, Leuconostoc and all gram-negative bacteria.

Teicoplanin when combined with aminoglycosides, bactericidal synergies against D group streptococci and staphylococci have been demonstrated *in vitro*. The *in vitro* combination of

teicoplanin with rifampicin or fluoroquinolones shows primarily additive effect and sometimes synergy.

Single-step resistance against to teicoplanin cannot be obtained *in vitro*, and multi-step resistance has been achieved *in vitro* only after 11-14 administrations.

Teicoplanin does not show cross-resistance to other classes of antibiotics.

The use of teicoplanin may cause over-growth of non-sensitive organisms. In case of new infections caused by bacteria or fungus during treatment, necessary precautions should be taken.

Sensitivity test
Sensidiscs are loaded with 30 micrograms of teicoplanin. The strains exhibiting an inhibition site of 14 mm or greater are sensitive, exhibiting an inhibition site of 10 mm or less are resistance.

5.2 Pharmacokinetic properties

General properties:
Absorption:
Teicoplanin is administered by parenteral injection. The bioavailability of intramuscular injection of 3-6 mg/kg is over 90%. Following oral administration, teicoplanin cannot be systemically absorbed from the normal gastrointestinal tract, and 40% of the administered dose is found in the faeces in a microbiological active form.

Distribution:
Teicoplanin rapidly penetrates the tissues after injection and reaches the highest concentrations in the kidney, trachea, lungs and adrenal glands by spreading into the skin (subcutaneous fat) and blister fluid, myocardium, pulmonary tissue and pleural fluid, bone and synovial fluid; penetrates neutrophils and strengthens bactericidal effects. Does not penetrate the red blood cells. Teicoplanin does not penetrate the cerebrospinal (CSF) fluid.

After intravenous administration in humans, the plasma level follows a biphasic distribution (a rapid distribution phase with a half-life of about 0.3 hours, followed by a longer distribution phase with a half-life of about 3 hours).
Teicoplanin binds to plasma proteins with a weak affinity of about 90 to 95%. The equilibrium distribution volume after the intravenous dose of 3-6 mg/kg is between 0.94 L/kg and 1.4 L/kg.
The distribution volume in children is not significantly different from that in adults.

Biotransformation
Following intravenous administration of 3-6 mg/kg, the plasma half-life with the terminal half-life is reduced to approximately 150 hours; total plasma clearance ranges from 11.9 mL/h/kg to 14.7 mL/h/kg. This long half-life allows one application per day.

At the end of intravenous administration of 6 mg/kg intravenously at 0., 12., 24. hours and once at every 24 hours for 30 minutes, the predicted 10 mg/mL serum concentration is seen on the 4th day. Estimated equilibrium peaks and serum concentrations of approximately 64 mg/mL and 19 mg/mL respectively, are obtained at day 28.

The teicoplanin metabolite was not detected; 97% of the applied teicoplanin is excreted unchanged.

Elimination:
The phase of biphasic distribution observed after intravenous administration is followed by a slow elimination. Following the oral administration, teicoplanin cannot be systemically absorbed from the normal gastrointestinal tract, and 40% of the administered dose is found in the faeces in a microbiological active form.
Renal clearance after an intravenous dose of 3-6 mg/kg is 10.4 - 12.1 mL/h/kg.
While 80% of the administered dose is excreted in the urine, the metabolic transformation is minimal, about 3%.

5.3 Preclinical safety data
Data obtained from preclinical studies showed that teicoplanin had a relatively low acute toxicity; In dogs (at a dose of 750 mg/kg), in rats (at a dose of 106 mg/kg) and in mice (at a dose of 715 mg/kg), and high LD50 values were obtained in studies performed with intravenous administration. These values are much higher than the treatment doses applied to people and it showed that the treatment range is wide.

Teicoplanin was well tolerated in chronic and subacute toxicity studies. In addition, it has been proven to show no mutagenic and teratogenic effect; abnormal effect on fertility, reproductive ability or peri and postnatal development was not observed. Sensitizing studies in rats, mice and guinea pigs did not show any sensitizing potential of the active substance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Vial: Sodium chloride, water for injection and sodium hydroxide / hydrochloric acid as pH adjuster

Ampoule: Water for injection

6.2 Incompatibilities
Teicoplanin solutions and aminoglycosides are incompatible when mixed directly and should not be mixed before injection.

6.3 Shelf Life
24 months

Storage conditions and duration after reconstitution: Store at 2-8°C in the refrigerator for 24 hours, do not freeze. Solutions that have been kept for more than 24 hours should not be used.

6.4 Special precautions for storage
Store at temperature below 25°C and in its own packaging.

6.5 Nature and contents of container
Each packaging contains a vial and an ampoule.

Vial: Colorless Type I glass vial sealed with a Bromobutyl rubber plug and transparent flip-off protective cap

Ampoule: Colorless, Type I glass ampoule

6.6 Special precautions for disposal and other handling

Unused products or waste materials must be disposed of in accordance with the local regulations.

Preparation:

1. Draw the entire water in the ampoule into an injector.

2. Remove the transparent plastic cap of the vial by pushing it up slightly.

3. Inject all of the water into the vial SLOWLY; approximately 0.2 ml of water will remain in the injector.

4. Roll the vial gently between both two hands until the powder inside is completely dissolved; Take care to avoid effervescence formation. IT MUST BE ENSURED THAT ALL POWDERS EVEN THE POWDERS LEFT AROUND THE RUBBER PLUG LINE IS COMPLETELY DISSOLVED.

Shaking this solution will lead to the formation of foam, making it difficult to draw the expected volume into the injector. However, if TEİKOPOL is fully dissolved, effervescence formation does not change the concentration of the solution and 100 mg for 1.5 ml or 200 mg for 3 ml (200 mg vial) or 400 mg for 3 ml (400 mg vial) concentrations are obtained. If effervescence is formed in solution, it is necessary to wait for 15 minutes.

5. Gently draw the solution from the vial to the injector by placing the needle in the middle of the rubber plug and trying to take most of the TEİKOPOL solution.
6. The concentration of a carefully prepared solution will be100 mg (200 mg vial) in 1.5 ml, 200 mg (200 mg vial) in 3 ml and 400 mg (400 mg vial) in 3 ml. It is important that the solution is properly prepared and carefully drawn into the syringe. Applications without carefully prepared preparations lead to administer lower than 50% of the doses.

7. The final solution is an isotonic solution with a pH between 7.2 and 7.8.

8. The reconstituted solution may be injected either directly or by diluting with followings:

- 0.9% Sodium chloride injection
- Sodium lactate compound injection (Ringer's Lactate solution, Hartmanns solution)
- 5% Dextrose injection
- Injection of 0.18% Sodium chloride and 4% Dextrose
- Peritoneal dialysis solutions containing 1.36% or 3.86% dextrose.

TEİKOPOL and aminoglycoside solutions are not compatible when mixed directly, they should not be mixed before injection.

9. Vial contents dissolved with distilled water should be stored in the refrigerator at 2-8°C for 24 hours and should not be frozen. Solutions that have been kept for more than 24 hours should not be used.

7. MARKETING AUTHORISATION HOLDER

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