MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

INSTRUCTION
for Medical Use of Pharmaceutical Products

VANCOMYCIN-TF
Powder for Solution
for Infusions 500 mg, 1,000 mg

Stamp: [APPROVED
by the Ministry of Health of the Republic of Belarus
Order of the Ministry of Health of the Republic of Belarus
No. *742* dd. *16.07.2015*]

Stamp: [TripleFarm, JLLC
Department for Development, Registration and Standardization
MASTER COPY]

Trade name Vancomycin-TF.
International nonproprietary name Vancomycin.
Pharmaceutical form Powder for solution for infusions 500 mg, 1,000 mg.
Appearance White or whitish powder.
Composition per 1 vial
Vancomycin (as vancomycin hydrochloride) – 500 mg equivalent to no less than 525,000 IU
Vancomycin (as vancomycin hydrochloride) – 1,000 mg equivalent to no less than 1,050,000 IU
Pharmacotherapeutic group Antibacterials for systemic use. Glycopeptide antibiotic.
ATC Code J01XA01.
Pharmacological properties
Pharmacodynamics
Vancomycin-TF is a tricyclic glycopeptide derived from Amycolatopsis orientalis. Antibacterial effect of Vancomycin-TF is inhibition of bacteria cell-wall biosynthesis. Antibiotic may alter bacterial cell membrane permeability and RNA synthesis.
Vancomycin-TF is active against *gram-positive microorganisms*: Staphylococcus spp. (including Staphylococcus aureus and Staphylococcus epidermidis, such as methicillin-resistant strains), Streptococcus spp. (including Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus viridans), Enterococcus spp. (including Enterococcus faecalis), Listeria spp., Lactobacillus spp., Corynebacterium diphtheriae, Clostridium spp., Actinomyces spp. There is no cross-resistance between Vancomycin-TF and other classes of antibiotics.
The minimum suppressing concentration for most antibiotic-sensitive microorganisms is less than 5 mcg/ml, the minimum suppressing concentration for tolerable Staphylococcus aureus is within 10 mcg/ml – 20 mcg/ml.
In vitro Vancomycin-TF is not active against *gram-negative microorganisms* (Chlamydia spp., Mycoplasma spp., Rickettsia spp.), fungi, mycobacteria. Resistance to Enterococcus faecium may develop.
Pharmacokinetics
Absorption
After oral administration Vancomycin-TF is poorly absorbed from gastro-intestinal tract. After intravenous injection of Vancomycin-TF in dose of 500 mg or 1 g mean plasma concentrations equal 50-60 mcg/ml and occur in 1 hour after infusion. In 12 hours after infusion Vancomycin-TF plasma concentration equals 5-10 mcg/ml.
Distribution

After intravenous injection antibiotic is present in pleural, pericardial, ascitic and synovial fuilds and atrial appendage tissue, and also in urine and peritoneal fluid in concentrations inhibiting microbial growth. Vancomycin-TF slowly penetrates cerebrospinal fluid. At meningitis the drug penetrates cerebrospinal fluid. Vancomycin-TF crosses the placental barrier and is excreted with breast milk. If vancomycin serum concentration is 10-100 mg/l, its protein binding equals 30-55%.

Metabolism and elimination

There is no apparent metabolism of the drug. Renal elimination by glomerular filtration accounts for 75-90% of the drug. From 40% to 100% of the injected dose is eliminated unchanged in urine. Vancomycin-TF may be insignificantly excreted with bile. In small amounts may be eliminated at haemodialysis or peritoneal dialysis. Elimination half-life of Vancomycin-TF equals 4.7-11.2 hours in patients with normal renal function.

Pharmacokinetics in particular medical cases

Renal dysfunction slows elimination of Vancomycin-TF. In anephric patients, the average half-life of elimination equals 7.5 days. The total systemic and renal clearance of Vancomycin-TF may be reduced in older patients due to the natural decrement of glomerular filtration.

Indications

Severe life-threatening Inflammatory infections induced by microorganisms sensitive to the medicine: endocarditis, sepsis, infections of bones and joints (including osteomyelitis), lower respiratory tract infections (pneumonia), skin and soft tissue infections, pseudo-membranous colitis, enterocolitis. Vancomycin-TF is used in cases of hypersensitivity to penicillin, intolerance or resistance to other antibiotics, including penicillins and cephalosporins.

Contraindications

Hypersensitivity to glycopeptides, first trimester of pregnancy, and cochlear neuritis.

With caution Vancomycin-TF should be prescribed in case of renal failure.

Warnings and precautions

Pregnancy and lactation

Vancomycin-TF should be administered in *the 2nd-3rd trimester of pregnancy* only in critical situations when potential benefits for mother outweighs the possible risk for fetus. If administered, the significant dose increase may be required for achievement of therapeutic serum concentration. If it is necessary to administer the drug *during lactation*, breastfeeding should be discontinued.

Special warnings

It is advised to administer Vancomycin-TF only under inpatient treatment. The drug should be infused slowly (not less than 60 min). Rapid Vancomycin-TF infusion may be associated with exaggerated hypotension and rarely, cardiac arrest. Due to painful infusions and possible tissue necrosis *intramuscular and intravenous bolus administration of Vancomycin-TF is not allowed*!

Frequency and severity of thrombophlebitis can be minimized by due dilution of the initial solution and by rotating the sites of infusion.

Prolonged Vancomycin-TF administration and associated drug administration causing neutropenia requires monitoring of leukocyte quantity.

Vancomycin infusion abdominally or by continuous outpatient peritoneal dialysis may cause chemical peritonitis syndrome, which ceases after drug administration is discontinued.

With caution Vancomycin-TF should be administered by the older people (over 60 years old). In these patients it is advised to monitor serum concentration of Vancomycin-TF. Patients hypersensitive to teicoplanin may suffer allergic cross reactions.

Due to its potential ototoxicity and nephrotoxicity Vancomycin-TF should be used with care in patients with renal insufficiency and hearing disorder. In such patients, it is advised to monitor constantly the level of vancomycin in blood for preventing toxic concentrations.

Prolonged use of Vancomycin-TF increases the risk of antibiotic-associated diarrhea and the risk of overgrowth of non-sensitive organisms.

Simultaneous administration of Vancomycin-TF with chloramphenicol, glucocorticoid drugs, methicillin, heparin, aminophylline, cephalosporins and phenobarbital *is not recommended*.
Vancomycin-TF may be administered orally only for treatment of staphylococcal enterocolitis and pseudomembranous colitis due to Clostridium difficile.
Use in paedtiatrics
In *infants* it is required to monitor serum concentrations of Vancomycin-TF.

Administration and dosage

Intramuscular and intravenous bolus administration of Vancomycin-TF is not allowed!
Vancomycin-TF is administered only by infusion. The following daily doses are recommended.
For *adults and children over 12 years of age* the dose is 500 mg intravenously every 6 hours or 1 g every 12 hours. The drug is administered by slow infusion with the rate of no more than 10 mg/min within 60 minutes or more. Concentration of Vancomycin-TF solution should not exceed 5 mg/ml. The maximum daily dose equals 2 g.
For *neonates under 7 days of age* the initial dose equals 15 mg/kg, then 10 mg/ml every 12 hours. For *infants from 7 up to 30 days of age* the initial dose equals 15 mg/kg, then 10 mg/ml every 8 hours. For *infants and children from 1 month up to 12 years of age* the recommended dose equals 10 mg/kg every 6 hours (total daily dose 40 mg/kg). Infusion lasts 60 minutes.
In *premature neonates* vancomycin clearance decreases with decrease of postconceptual age. Thus for this group of patients intervals between doses should be increased and vancomycin serum concentration should be monitored carefully.

Vancomycin dosage for premature neonates			
PCA[a]	Chronological age (days)	Serum creatinine concentration (mg/dl)[b]	Dose (mg/kg)
< 30	≤ 7	–[c]	15 every 24 hours
	> 7	≤ 1.2	10 every 10 hours
30-36	≤ 7	–[c]	10 every 12 hours
	> 7	≤ 0.6	10 every 8 hours
		0.7-1.2	10 every 12 hours
> 36	≤ 7	–[c]	10 every 12 hours
	> 7	≤ 0.6	10 every 8 hours
		0.7-1.2	10 every 12 hours

a – PCA – postconceptual age (gestation age at birth plus chronological age).
b – if the serum creatinine concentration is > 1.2 mg/dl, an initial dosage of 15 mg/kg is used every 24 hours.
c – creatinine concentration is not used to determine the dosage for this type of patients because of the lack of information.
For *patients with impaired renal function* the dose should be adjusted individually.
For the avoidance of toxic concentrations, doses should be adjusted and serum concentration of vancomycin should be monitored.
The table represents dose adjustment scheme depending on creatinine clearance.

Creatinine clearance, ml/min	Vancomycin-TF dose, mg/day
100	1,545
90	1,390
80	1,235
70	1,080
60	925
50	770
40	620
30	465
20	310
10	155

The initial dose should be not less than 15 mg/kg even in patients with minor and moderate renal failure. This table is not valid for anephric patients on dialysis. For such patients recommended initial dose is 15 mg/kg, and maintenance dose is 1.9 mg/kg/24 hours. Patients with marked renal failure are advised to administer maintenance doses from 250 up to 1,000 mg once every several days instead of daily. In anuria a recommended dose equals 1,000 mg every 7-10 days.

If polysulfone membranes are used for haemodialysis ("high flux dialysis") vancomycin elimination time is reduced. For patients with regular haemodialysis additional maintenance dose may be required.

If renal function is unstable, creatinine clearance-adjusted evaluation will be unreliable. For patients with impaired renal function due to shock, severe heart failure or oliguria; for obese patients or patients suffering hepatic diseases, edemas or ascites; for fragile patients with eating or motor disorders intermittent infusions are advised.

Older patients and premature neonates due to the impairment of renal function may require reduced dose or increase of intervals between infusions.

The duration of treatment with Vancomycin-TF depends on the infection severity, and clinical and bacteriologic treatment results.

Patients with hepatic failure should be treated regular doses with no modifications.

For the treatment of staphylococcus entercolitis and pseudomembranous colitis due to Clostridium difficile Vancomycin-TF is administered orally. Regular daily dose for oral administration *by adults* is from 500 mg to 1 g, *by children* – 40 mg/kg of bodyweight divided into 3-4 intakes; treatment lasts 7-10 days. It is not recommended to exceed daily dose of 2 g.

Monitoring of vancomycin serum concentrations

Vancomycin serum concentration should be monitored starting from the second day of treatment, immediately prior the dose infusion and in an hour after the infusion. Therapeutic concentrations of vancomycin should range from 30 and 40 mg/ml (max 50 mg/ml) in an hour after infusion, 18-26 mg/ml in 2 hours, minimum value prior the next infusion should be 5-10 mg/ml. Concentrations should be monitored 2-3 times a week.

Rules for solution preparation and infusion

Preparation of solution for intravenous administration. Solution is prepared immediately prior drug administration. For preparation of Vancomycin-TF solution with concentration of 50 mg/ml the necessary amount of solvent is added to the vial (10 ml to the vial containing 500 mg of Vancomycin-TF and 20 ml to the vial containing 1 g). Derived solution is subject to further dilution in 100 ml or 200 ml of solvent up to the concentration of no more than 5 mg/ml. Water for injections, 0.9% saline solution for injections or 5% glucose solution for injections may be used as solvents.

Preparation of solution for oral administration. Recommended dose of Vancomycin-TF is diluted in 30 ml of water. Derived solution may be prescribed for drinking or given to the patient using the probe. Edible syrups may be used to improve taste of solution.

Side effects

Digestive disorder: nausea, vomiting, diarrhea (severe diarrhea may be the symptom of superinfection by resistant microorganisms or development of pseudomembranous colitis).

Blood and lymphatic system disorder: reversible neutropenia, leukopenia, eosinophilia, thrombocytopenia, rarely, agranulocytosis.

Urinary disorder: nephrotoxicity, present as increase of creatinine and urea nitrogen serum concentrations (in case of large dose of Vancomycin-TF administration); rarely, interstitial nephritis (in patients given aminoglycoside antibiotics concomitantly or who had pre-existing renal dysfunction). When Vancomycin-TF is discontinued, in most patients renal function normalizes and azotaemia resolves.

Allergic reactions: Stevens-Johnson syndrome , toxic epidermal necrolysis, vasculitis, drug rash with eosinophilia and systemic symptoms.

CNS disorder: vertigo, including vestibular, hearing impairment.

Local reactions: if infusion rules are breached, thrombophlebitis, tissue necrosis at the infusion site.
Rapid drug infusion may cause postinfusion reactions: anaphylactoid reactions (hypotension, vertigo, rapid hear palpitation, bronchospasm, fever), skin rush, "red-neck" syndrome (hyperemia of the upper body), muscle spasm of the neck or back. After discontinuation of infusion these reactions may resolve in 20 minutes, but sometimes persist for several hours.

Overdose

Symptoms: increase of side effects severity.
Treatment: the drug is discontinued or the dose is reduced. Symptomatic therapy is carried out. Injection of liquid and monitoring of serum concentrations of Vancomycin-TF are advised. For rapid removal of Vancomycin-TF excess from the body hemofiltration is more effective than haemodialysis.

Interaction with other medicinal products

Concomitant administration of Vancomycin-TF and other potentially neurotoxic and/or nephrotoxic drugs (etacrynic acid, aminoglycoside antibiotics, cisplatin, amphotericin B, bacitracin, polymixin B, colistin, viomycin) may cause mutual enhancement of their toxic effect, which requires careful monitoring of possible development of such symptoms. There is higher risk of extension of neuromuscular block at concurrent administration of muscle relaxants.
Vancomycin-TF should not be administered simultaneously with ototoxic drugs due to possible increase of ototoxic effect.
At concurrent administration of Vancomycin-TF and histamine antagonists, the latter may conceal symptoms of Vancomycin-TF ototoxic effect (buzzing, vertigo).
At simultaneous administration of Vancomycin-TF and anaesthetic agents the risk of arterial hypotension, erythema, urticaria or itching increases, and also anaphylactoid reactions are possible.
Pharmaceutical incompatibility
Vancomycin-TF solution has low pH, which may result in physical or chemical instability during mixing with other solutions. Mixing with alkaline solutions should be avoided.

Storage and shelf life

Keep secured from light at temperature from 2° C up to 8° C.
Keep out of the reach of children.
Shelf life equals 2 years. Do not use after the expiry of shelf life specified on the package.

How dispensed

Prescription use.

Package

500 mg in 10 ml vial.
5 vials per pack or 36 vials per box (package for inpatient hospitals).
1,000 mg in 20 ml vial.
5 vials per pack or 25 vials per box (package for inpatient hospitals).

Manufacturer

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