Package Insert

Vangacin 500

Vangacin 1 G

1. **Product Name**

   Vangacin 500

   Vangacin 1 G

2. **Name and Strength of Active Ingredient(s)**

   Each vial contains:-

   Vancomycin Hydrochloride eq. to Vancomycin 500 mg

   Vancomycin Hydrochloride eq. to Vancomycin 1 g

3. **Product Description**

   White to off-white sterile powder

4. **Pharmacodynamics and Pharmacokinetics**

   Pharmacodynamics

   The bactericidal action of vancomycin, a tricyclic glycopeptide antibiotic, results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial cell membrane permeability and RNA synthesis. It is bactericidal against a number of aerobic and anaerobic gram-positive microorganisms and it is synergistic when combined with another antibiotic.

   Pharmacokinetics

   Absorption - In subjects with healthy kidney function, multiple IV dosing of vancomycin 1 g (15 mg/kg) infused over 60 minutes produces mean plasma concentrations of approximately 63 mcg/mL immediately after the completion of infusion, mean plasma concentrations of approximately 23 mcg/mL 2 hours after infusion, and mean plasma concentrations of approximately 8 mcg/mL 11 hours after the end of the infusion.

   Multiple dosing of 500 mg infused over 30 minutes produces mean plasma concentrations of about 49 mcg/mL at the completion of infusion, mean plasma concentrations of about 19 mcg/mL 2 hours after infusion, and mean plasma concentrations of about 10 mcg/mL 6 hours after infusion. The plasma concentrations during multiple dosing are similar to those after a single dose.

   Distribution – Vancomycin is approximately 55% serum protein bound as measured by ultrafiltration at vancomycin serum concentrations of 10 to 100 mcg/mL. The distribution coefficient is from 0.3 to 0.43 L/kg. After IV administration of vancomycin, inhibitory concentrations are present in pleural, pericardial, ascitic, and synovial fluid; in urine, in peritoneal dialysis fluid; and in atrial appendage tissue. Vancomycin does not readily

diffuse across healthy meninges into the spinal fluid, but when meninges are inflamed, penetration into the spinal fluid occurs.

Metabolism/excretion – The mean elimination half-life of vancomycin from plasma is 4 to 6 hours in subjects with healthy renal function. In the first 24 hours, about 75% of an administered dose of vancomycin is excreted in urine by glomerular filtration. Mean plasma clearance is about 0.058 L/kg/h, and mean renal clearance is about 0.048 L/kg/h. There is no apparent metabolism of the drug.

5. Indication

- Endocarditis:

  Diphtheroid - For the treatment of diphtheroid endocarditis. Vancomycin has been used successfully in combination with either rifampin, an aminoglycoside or both in early-onset prosthetic valve endocarditis caused by *Staphylococcus epidermidis* or diphtheroids.

  Enterococcal - For endocarditis caused by enterococci (e.g., *Enterococcus faecalis*), vancomycin has been reported to be effective only in combination with an aminoglycoside.

  Staphylococcal - In the treatment of *Staphylococcal endocarditis*.

  Streptococcal - Alone or in combination with aminoglycoside for endocarditis caused by *Streptococcus viridans* or *Streptococcus bovis*.

- *Clostridium difficile*-associated diarrhea/ *Staphylococcal enterocolitis*: Certain parenteral products of vancomycin may be administered orally for treatment of *C. difficile*-associated diarrhea and for *Staphylococcal enterocolitis*. Parenteral administration of vancomycin alone is of unproven benefit for these indications. Vancomycin is not effective by the oral route for other types of infection.
- *Staphylococcal* infections: For the treatment of serious or severe infection caused by susceptible strains of methicillin-resistant (beta-lactam-resistant) staphylococci. It is indicated for patients who are allergic to penicillin; for patients who cannot receive or who have failed to respond to other drugs, including the penicillins or cephalosporins; and for infections caused by vancomycin-susceptible organisms that are resistant to other antimicrobial drugs. Vancomycin is indicated for initial therapy when methicillin-resistant staphylococci are suspected, but after susceptibility data are available, adjust therapy accordingly.

  Its effectiveness has been documented in other infections due to staphylococci, including septicemia, bone infections, lower respiratory tract infections, and skin and skin structure infections. When *staphylococcal* infections are localized and purulent, antibiotics are used as adjuncts to appropriate surgical measures.
- Vancomycin is recommended for the treatment of mild, moderate, and severe *Clostridium difficile* infections in pregnant women.

- Vancomycin is recommended as an alternative agent to prevent the transmission of group B streptococcal (GBS) disease from mothers to newborns.
- Vancomycin is used for prevention of bacterial endocarditis. It is used as an alternative agent for prevention of enterococcal endocarditis in penicillin-allergic adults and children with congenital heart disease, rheumatic or other acquired valvular heart dysfunction, prosthetic heart valves, who undergo certain GI, biliary tract, or genitourinary surgery of instrumentation likely to cause transient bacteremia and increase the risk of endocarditis. The AHA recognizes that its current recommendations for prophylaxis against bacterial endocarditis are empiric, since no controlled efficacy studies have been published. However, the AHA generally recommend routine use for prophylactic anti-infectives in patients with the cardiac conditions described above since these are associated with a high or moderate risk for bacterial endocarditis.
- Prophylaxis against infective endocarditis: Dental, oral, or upper respiratory tract surgery. American Heart Associate (AHA) guidelines recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur.

6. Recommended Dose

Adult:

- Endocarditis – 500 mg intravenously (IV) every 6 hours or 1 g IV every 12 hours
- *C. difficile*-associated diarrhea/ *staphylococcal enterocolitis* – 500 mg to 2 g orally daily given in 4 divided doses for 7 to 14 days. (See Preparation for administration)
- *Staphylococcal* infections – usual 500 mg IV every 6 hours or 1 g IV every 12 hours

Pediatric:

- Endocarditis –1 month and older: 10 mg/kg/dose IV given every 6 hours.

  Up to 1 month of age: The total daily IV dosage may be lower.

  In neonates, an initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the first week of life and every 8 hours thereafter up to 1 month of age.

  In premature infants, vancomycin clearance decreases as postconceptional age decreases. Therefore, longer dosing intervals may be necessary in premature infants.
- Pseudomembranous colitis/ *staphylococcal enterocolitis* – Usual dosage: 40 mg/kg/day given orally in 3 or 4 divided doses for 7 to 10 days. (See Preparation for administration) Maximum dose: 2 g/ day
- *Staphylococcal* infections – usual dosage: 1 month and older: 10 mg/kg/dose IV given every 6 hours.

Up to 1 month of age: The total IV dosage may be lower. An initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the first week of life and every 8 hours thereafter up to the age of 1 month.

In premature infants, vancomycin clearance decreases as postconceptional age decrease. Therefore, longer dosing interval may be necessary in premature infants.

- Prophylaxis against infective endocarditis: Children and adolescents: IV: Dental, oral, or upper respiratory tract surgery: 20 mg/kg/dose administered 1 hour prior to the procedure

Elderly:

Vancomycin dosage schedules should be adjusted in elderly patients. Greater dosage reductions than expected may be necessary because of decreased renal function.

Renal function impairment:

Initial dose – The initial dose should be no less than 15 mg/kg even in patients with mild to moderate renal insufficiency.

Dosage adjustment – Dosage adjustment must be made in patients with impaired renal function. In premature infants and elderly patients, greater dosage reductions than expected may be necessary because of decreased renal function. Measurement of vancomycin serum concentration can be helpful in optimization therapy, especially in seriously ill patients with changing renal function.

If creatinine clearance (CrCl) can be measured or estimated accurately, the dosage for most patients with renal impairment can be calculated using the following data. The dosage of vancomycin per day in milligrams is about 15 times the glomerular filtration rate (GFR) in mL/min.

Vancomycin Dosage for Patients with Renal Function Impairment	
CrCl	Vancomycin dose
100 mL/min	1,545 mg per 24h
90 mL/min	1,390 mg per 24h
80 mL/min	1,235 mg per 24h
70 mL/min	1,080 mg per 24h
60 mL/min	952 mg per 24h
50 mL/min	770 mg per 24h
40 mL/min	620 mg per 24h
30 mL/min	465 mg per 24h
20 mL/min	310 mg per 24h
10 mL/min	155 mg per 24h

In patients with marked renal impairment, it may be more convenient to give maintenance doses of 250 to 1,000 mg once every several days rather than administering the drug on a daily basis.

Indication-specific dosing:

Adult & Geriatric:

- Pneumonia, *S. aureus* (methicillin-resistant):

- Community-acquired pneumonia (CAP): 15 to 20 mg/kg/dose (based on actual body weight) every 8 to 12 hours for 7 to 21 days depending on severity.
- Hospital-acquired pneumonia or ventilation-associated pneumonia: 15 mg/kg/dose every 8 to 12 hours for 7 days; may consider shorter or longer duration depending on rate of clinical improvement. A loading dose of 25 to 30 mg/kg/dose may be used in seriously ill patients.

  When used as empiric therapy, use in combination with an antipseudomonal agent (one or two antipseudomonal agents depending on patient and institution specific risk factors).

- Sepsis/Septic shock (empiric treatment or treatment for specific sensitive organism): IV: 15 to 20 mg/kg/dose (based on actual body weight) every 8 to 12 hours. A loading dose of 25 to 30 mg/kg (based on actual body weight) may be used to rapidly achieve target concentrations in seriously ill patients.

Pediatric:

- Meningitis: infants > 1 month, Children, and Adolescents: IV: 15 mg/kg/dose every 6 hours (for empiric therapy, use in combination with a third-generation cephalosporin); duration of therapy should be individualized based upon clinical response. For methicillin -resistant *S. aureus*, treat for 2 weeks (with or without rifampin).

- Pneumonia:

- Community-acquired pneumonia (CAP): infants > 3 month, Children, and Adolescents: IV: Note: In children $\geq$ 5 years, a macrolide antibiotic should be added if atypical pneumonia cannot be ruled out. Also consider if community-acquired MRSA suspected.
- Group A *Streptococcus* (alternative to ampicillin or penicillin in beta-lactam allergic patients):

  40 to 60 mg/kg/day divided every 6 to 8 hours.
- Presumed bacterial (in addition to recommended antibiotic therapy), *S. pneumoniae*, moderate to severe infection (MICs to penicillin $\leq$ 2.0 mcg /mL) (alternative to ampicillin or penicillin):

  40 to 60 mg/kg/day divided every 6 to 8 hours.
- *S. aureus* (methicillin -susceptible) (alternative to cefazolin/oxacillin): 40 to 60 mg/kg/day divided every 6 to 8 hours.

- *S. aureus*, moderate to severe infection (methicillin-resistant +/- clindamycin susceptible) (preferred): 40 to 60 mg/kg/day divided every 6 to 8 hours or dosing to achieve AUC/MIC > 400.

  Alternate regimen: 60 mg/kg/day divided every 6 hours for 7 to 21 days, depending on severity.
- *S. pneumoniae*, moderate to severe infection (MICs to penicillin $\geq$ 4.0 mcg/mL) (alternative to ceftriaxone in beta-lactam allergic patients): 40 to 60 mg/kg/day divided every 6 to 8 hours.
- Healthcare-associated pneumonia (HAP), *S. aureus* (methicillin -resistant): IV: Infants, Children, and Adolescent: 60 mg/kg/day divided every 6 hours for 7 to 21 days depending on severity.

- Prophylaxis against infective endocarditis: Children and Adolescents: IV:

- Dental, oral, or upper respiratory tract surgery: 20 mg/kg/dose administered 1 hour prior to the procedure. Note: American Heart Associate (AHA) guidelines recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur.
- GI/GU procedure: 20 mg/kg (plus gentamycin 1.5 mg/kg) administered 1 hour prior to surgery. Note: Routine prophylaxis no longer recommended by the AHA.

7. Mode of Administration

Intermittent infusion is the recommended method of administration. Vancomycin hydrochloride is administered by slow IV infusion for the treatment of systemic infections. Vancomycin is very irritating to tissue and must not be given IM. Safety and efficacy of intrathecal (intralumbar or intraventricular) or intraperitoneal administration of vancomycin have not been determined. Vancomycin hydrochloride usually is administered by intermittent IV infusion but has been administered by continuous IV infusion when intermittent infusions were not feasible. Vangacin 500 and Vangacin 1 G are administered by intermittent IV infusion or continuous IV infusion.

<u>Preparation for administration</u>

Powder for IV infusion solution – At the time of use, reconstitute by adding 10 mL of sterile water for injection or 5% dextrose injection or 0.9% sodium chloride injection to the 500 mg vial, 20 mL of sterile water for injection or 5% dextrose injection or 0.9% sodium chloride injection to the 1 g vial.

Reconstituted solutions containing vancomycin 500 mg must be diluted with at least 100 mL of diluent. Reconstituted solutions containing vancomycin 1 g must be diluted with at least 200 mL of diluent.

Administer vancomycin in concentration of no more than 5 mg/mL.

Admixture compatibilities

Compatibility- The following diluents are physically and chemically compatible with vancomycin: Dextrose 5% injection, dextrose 5% injection and sodium chloride 0.9% injection, Ringer's lactate injection, dextrose 5% and ringer's lactate injection, *Normosol-M* and dextrose 5%, Sodium chloride 0.9% injection, and *Isolyte E.*

Incompatibility – Mixtures of solutions of vancomycin and beta-lactam antibiotics have been shown to be physically incompatible. The likelihood of precipitation increases with higher concentrations of vancomycin. It is recommended to adequately flush the IV lines between the administration of these antibiotics. It is recommended to dilute solutions of vancomycin to 5 mg/mL or less.

Vancomycin solution has a low pH and may cause chemical or physical instability when it is mixed with other compounds.

Storage/ Stability

After initial reconstitution with sterile water for injection, Dextrose 5% injection, or Sodium chloride 0.9% injection, solution are stable for 14 days if refrigerated. After further dilution with dextrose 5% injection or Sodium chloride 0.9% injection, the solution may be stored in a refrigerator for 14 days without significant loss of potency.

Solution dilute with dextrose 5% and Sodium chloride 0.9% injection, Ringer's lactate injection, Ringer's lactate injection and dextrose 5% injection, or *Normosol-M* and dextrose 5% may be stored in a refrigerator for 96 hours.

Rate of administration

- Administer vancomycin at rate no more than 10 mg/min or over a period of at least 60 minutes, whichever is longer.
- Intermittent IV infusion of vancomycin should be given over a period of at least 1 hour.
- Rapid infusion (e.g., over several minutes) should be avoided, and patients should be monitored closely during infusion of the drug. However, to minimize adverse effect, vancomycin should be administered IV at a rate not exceeding 10 mg/min.

Parenteral drug product should be inspected visually for particle matter and discoloration prior to administration, whenever solution and container permit.

8. Contraindication

Hypersensitivity to vancomycin

9. Warnings/ precautions

Warnings base on the Ministry of Public Health Announcement

- Do not use in hypersensitive patients.
- In pregnant women, vancomycin may cause ear nerve damage in fetus.

Warnings/ precautions

- Administration: Rapid bolus administration (e.g., several minutes) may be associated with exaggerated hypotension, including shock and, rarely, cardiac arrest.
- Ototoxicity: Ototoxicity has occurred in patients receiving vancomycin. It may be transient or permanent. It has been reported mostly in patients who have been excessive dose, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside.
- *C. difficile*-associated diarrhea: *C. difficile*-associated diarrhea has been reported with nearly all antibacterial agents, including vancomycin, and may range in severity from mild diarrhea to fatal colitis.
- Neutropenia: Reversible neutropenia, usually starting 1 week or more after onset of therapy with vancomycin or after a total dosage of more than 25 g, has been reported in patients receiving vancomycin.
- Tissue irritation: Vancomycin is irritating to tissue and must be given by a secure IV route of administration. Pain, tenderness, and necrosis occur with IM injection of vancomycin or with inadvertent extravasation. Thrombophlebitis may occur, the frequency and severity of which can be minimized by administering the drug slowly as a dilute solution (2.5 to 5 g/L) and by rotating the sites of venous access.
- Hypersensitivity reactions: During or soon after the rapid infusion of vancomycin, patients may develop anaphylactoid reactions, including dyspnea, hypotension, pruritus, urticaria, or wheezing. Rapid infusion may also cause flushing of the upper body (“red neck”) or pain and muscle spasm of the chest and back.
- Renal function impairment: Use vancomycin with caution in patients with renal insufficient because the risk of toxicity is appreciably increased by high, prolonged blood concentration.
- Superinfection: Prolonged use of vancomycin may result in the overgrowth of non-susceptible organisms.

10. Drug interaction

- Aminoglycoside: Vancomycin may enhance the nephrotoxic effect of Aminoglycoside.
- BCG: Antibiotic may diminish the therapeutic effect of BCG. Avoid combination
- Bile Acid Sequestrants: May diminish the therapeutic effect of Vancomycin.
- Colistimethate: Vancomycin may enhance the nephrotoxic effect of Colistimethate.
- Neuromuscular Blocking Agents: Vancomycin may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents.

- Nonsteroid Anti-inflammatory: Nonsteroid Anti-inflammatory may increase the serum concentration of Vancomycin.
- Piperacillin: Piperacillin may enhance the nephrotoxic effect of Vancomycin.
- Sodium Picosulfate: Antibiotic may diminish the therapeutic effect of Sodium Picosulfate.
- Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected.

11. Pregnancy and Lactation

- Pregnancy: Category C. Adverse events have not been observed in animal reproduction studies. Vancomycin crosses the placenta and can be detected in fetal serum amniotic fluid, and cord blood.

  Adverse fetal effects, including sensorineural hearing loss or nephrotoxicity, have not been reported following maternal use during the second or third trimesters of pregnancy. The pharmacokinetics of vancomycin may be altered during pregnancy and pregnant patients may be need a higher dose of vancomycin. Maternal half-life is unchanged, but the volume of distribution and the total plasma clearance may be increased.
- Lactation: Vancomycin is excreted in human milk following IV administration. Vancomycin is recommended for the treatment of mild, moderate, or severe *Clostridium difficile* infections in breast feeding women. Due to the potential for serious adverse reactions in the breast-feeding infant, the manufacturer recommends a decision be made whether to discontinue breast-feeding or to discontinue the drug, taking into account the importance of treatment to the mother.

12. Undesirable effects/ Adverse Reactions

- GI: onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.
- Hematologic: Reversible neutropenia, usually starting 1 week or more after onset of therapy with vancomycin or after a total dosage of more than 25 g, had been reported for several dozen patients. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been reported.
- Hypersensitivity: During or soon after the rapid infusion of vancomycin, patients may develop anaphylactoid reactions, including dyspnea, hypotension, pruritus, urticaria, or wheezing. Rapid infusion may also cause flushing of the upper body (“red neck”) or pain and muscle spasm of the chest and back.
- Local: Inflammation at the injection site has been reported.
- Renal: Rarely, renal failure, principally manifested by increased serum creatinine or serum urea nitrogen concentrations, especially in patients given large doses of vancomycin, has been reported. Rare cases of interstitial nephritis have been reported. Most of these have occurred in patients who were given aminoglycosides concomitantly or who had preexisting kidney dysfunction. When vancomycin was discontinued, azotemia resolved in most patients.

- Special sense: A few dozen cases of hearing loss associated with vancomycin have been reported. Most of these patients had kidney dysfunction or a preexisting hearing loss or were receiving concomitant treatment with an ototoxic drug. Dizziness, tinnitus, and vertigo have been reported rarely.
- Miscellaneous: Infrequently, patients have been reported to have had anaphylaxis, chills, drug fever, eosinophilia, nausea, rashes, (including exfoliative dermatitis) Stevens-Johnson syndrome, toxic epidermal necrolysis, and vasculitis in associated with administration of vancomycin.
- Dermatologic: drug rash with eosinophilia and systemic symptoms.

13. Over dosage and treatment

Over dosage

Three premature infants developed apnea, hypotension, flushed skin, and inflammation at the infusion site following inadvertent overdose of vancomycin (300 to 400 mg/kg).

Two premature infants with peak plasma vancomycin concentrations greater than 300 mcg/mL following inadvertent 10-fold overdoses did not experience any renal (except for one infant with a transient increase in serum creatinine to 1.4 mg/dL), auditory, or other toxicity.

Toxicity is reported at serum concentrations sustained above 80 to 100 mcg/mL.

Treatment

Management of mild to moderate toxicity: Treatment is symptomatic and supportive. Manage mild hypotension with IV fluids.

Management of severe toxicity: severe hypotension with IV 0.9% NaCl at 10 to 20 mL/kg. Add dopamine or norepinephrine if unresponsive to fluids.

Red Man Syndrome: Antihistamines can be used as pretreatment. Increasing the dilution of vancomycin and slowing the rate intravenous administration may also help.

Antidote: None

Enhanced elimination procedure: Enhanced elimination is generally only necessary in patients with severe renal insufficiency. Hemoperfusion, hemofiltration, high-flux hemodialysis, and hemodiafiltration have been effective in reducing serum vancomycin concentrations when high-porosity hemofilters are used.

Multiple dose activated charcoal (MDAC): May decrease the half-life of intravenously administered vancomycin but has not been shown to affect outcome. It is not routinely recommended but can be considered for patients with large overdoses when the patient is expected to have prolonged clearance, if the potential benefits are felt to outweigh risks. MDAC should not be administered in patients who are at risk for the abrupt onset of seizures or mental status depression or who are not able to protect airway.

14. Storage condition

Store below 30^{o} C

15. Dosage forms and packing available

Glass vial (Type I) with flip-off cap contains vancomycin hydrochloride eq. to vancomycin 500 mg or vancomycin hydrochloride eq. to vancomycin 1 g, packed or unpacked in a box of 1, 5, 10, 20, 25, 50 and 100 vials.

16. Name and address of manufacturing/ marketing authorization holder

ABLE MEDICAL COMPANY LIMITED

111 Moo. 9 Nongson, Chiangyuen,

Mahasarakham 44160, Thailand

17. Date of revision of package insert

12 June, 2023