

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VANKOPOL 1000 mg Lyophilized Powder for Solution for I.V. Infusion And Oral Use

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance: Each vial contains 1050 mg vancomycin hydrochloride (1.000.000 IU) equivalent to 1000 mg vancomycin

Excipient(s): For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Vial containing lyophilized powder for oral solution and solution for infusion

Vial contains a white or almost white lyophilized powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Intravenous administration

VANKOPOL is indicated in all age groups for the treatment of the following infections:

- Complicated skin and soft tissue infections
- Bone and joint infections
- Community acquired pneumonia
- hospital acquired pneumonia, including ventilator-associated pneumonia
- Infective endocarditis

It is also indicated in all age groups for the perioperative antibacterial prophylaxis in patients that are at high risk of developing bacterial endocarditis when undergoing major surgical procedures.

Oral use:

It is indicated in all age groups for the treatment of Clostridium difficile infections.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and method of administration

Posology:

Where appropriate, it can be administered in combination with other antibacterial agents.

Intravenous administration

The initial dose should be based on total body weight. Subsequent dose adjustments should be based on serum concentrations to achieve targeted therapeutic concentrations. Renal function must be taken into consideration for subsequent doses and interval of administration.

In children aged 12 years and older.

The recommended dose is 15 to 20 mg/kg of body weight every 8 to 12 h. The daily dose should not exceed 2 g.

In seriously ill patients, a loading dose of 25–30 mg/kg of body weight can be used to facilitate rapid attainment of target serum vancomycin concentration.

Infants and children aged from one month to less than 12 years of age:

The recommended dose is 10 to 15 mg/kg body weight every 6 hours.

Term neonates (from birth to 27 days of post-natal age) and preterm neonates (from birth to the expected date of delivery plus 27 days)

For establishing the dosing regimen for neonates, the advice of a physician experienced in the management of neonates should be sought. One possible way of dosing vancomycin in neonates is illustrated in the following table:

PMA (weeks)	Dose (mg/kg)	Interval (hour)
<29	15	24
29-35	15	12
>35	15	8

PMA: post-menstrual age [(time elapsed between the first day of the last menstrual period and birth (gestational age) plus the time elapsed after birth (post-natal age)].

Peri-operative prophylaxis of bacterial endocarditis in all age groups

The recommended dose is an initial dose of 15 mg/kg prior to induction of anesthesia. Depending on the duration of surgery, a second vancomycin dose may be required.

Duration of treatment

Suggested treatment duration is shown in table below. In any case, the duration of treatment should be tailored to the type and severity of infection and the individual clinical response.

Indication	Treatment duration
Complicated skin and soft tissue infections <i>- <u>Non necrotizing</u></i>	7 to 14 days
<i>- <u>Necrotizing</u></i>	4 to 6 weeks*

Bone and joint infections	4 to 6 weeks**
Community-Acquired Pneumonia	7 to 14 days
Hospital acquired pneumonia, including ventilator-associated pneumonia	7 to 14 days
Infective endocarditis	4 to 6 weeks***

*Continue until further debridement is not necessary, patient has clinically improved, and patient is afebrile for 48 to 72 hours.

**Longer courses of oral suppression treatment should be considered for prosthetic joint infections

***Duration and need for combination therapy is based on valve-type and organism

Additional information on special populations

Geriatric population

Lower maintenance doses may be required due to the age-related reduction in renal function.

Renal impairment

In adult and pediatric patients with renal impairment, consideration should be given to an initial starting dose followed by serum vancomycin levels rather than to a scheduled dosing regimen. Particularly in patients with severe renal impairment or those who undergo renal replacement therapy (RRT) caution is advised due to the many varying factors that may affect vancomycin levels.

In patients with mild or moderate renal failure, the starting dose must not be reduced. In patients with severe renal failure, it is preferable to prolong the interval of administration rather than administer lower daily doses.

Appropriate consideration should be given to the concomitant administration of medicinal products that may reduce vancomycin clearance and/or potentiate its undesirable effects.

Vancomycin is poorly dialyzable by intermittent hemodialysis. However, use of high-flux membranes and continuous renal replacement therapy (CRRT) increases vancomycin clearance and generally requires replacement dosing (usually after the haemodialysis session in case of intermittent haemodialysis).

Adults:

Dose adjustments in adult patients could be based on glomerular filtration rate estimated (eGFR) by the following formula:

Men: $[\text{Weight (kg)} \times 140 - \text{age (years)}] / 72 \times \text{serum creatinine (mg/dl)}$

Women: 0.85 x value calculated by the above formula.

The usual starting dose for adult patients is 15 to 20 mg/kg that could be administered every 24 hours in patients with creatinine clearance between 20 to 49 ml/min. In patients with severe renal impairment (creatinine clearance below 20 ml/min) or those on renal replacement therapy, the appropriate timing and amount of subsequent doses largely depend on the modality of RRT and should be based on serum vancomycin trough levels and on residual renal function. Depending on the clinical situation, consideration could be given to withhold the next dose while awaiting the results of vancomycin levels.

In the critically ill patient with renal insufficiency, the initial loading dose (25 to 30 mg/kg) should not be reduced.

Pediatric Population

Dose adjustments in pediatric patients aged 1 year and older could be based on glomerular filtration rate estimated

(eGFR) by the revised Schwartz formula:

$$eGFR \text{ (mL/min/1.73m}^2\text{)} = (\text{height cm} \times 0.413) / \text{serum creatinine (mg/dl)}$$

$$eGFR \text{ (mL/min/1.73m}^2\text{)} = (\text{height cm} \times 36.2) / \text{serum creatinine (mg/dl)}$$

For neonates and infants below 1 year of age, expert advice should be sought as the revised Schwartz formula is not applicable to them.

Orientative dosing recommendations for the pediatric population are shown in table below that follow the same principles as in adult patients.

GFR (ml/min/1.73m²)	IV dose	Frequency
50-30	15 mg/kg	Every 12 hours
29-10	15 mg/kg	Every 24 hours
<10	10-15 mg/kg	Re-dose based on levels*
Intermittent hemodialysis		
Peritoneal dialysis		
Continuous renal replacement treatment	15 mg/kg	Re-dose based on levels*

*The appropriate timing and amount of subsequent doses largely depends on the modality of RRT and should be based on serum vancomycin levels obtained prior to dosing and on residual renal function. Depending on the clinical situation, consideration could be given to withhold the next dose while awaiting the results of vancomycin levels.

Hepatic impairment

No dose adjustment is required in patient with hepatic failure.

Pregnancy

Significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant women.

Obese patients

In obese patients, the initial dose should be individually adapted according to total body weight as in non-obese patients.

Oral use

In children aged 12 years and older

Treatment of Clostridium difficile infection (CDI):

The recommended vancomycin dose is 125 mg every 6 hours for 10 days for the first episode of non-severe CDI. This dose can be increased to 500 mg every 6 hours for 10 days in case of severe or complicated disease. The maximum daily dose should not exceed 2 g.

In patients with multiple recurrences, consideration may be given to treat the episode of CDI with vancomycin, 125 mg four times daily for 10 days followed by either tapering the dose, i.e., gradually decreasing it until 125 mg per day or a pulse regimen, i.e., 125–500 mg/day every 2–3 days for at least 3 weeks.

Neonates, infants and children less than 12 years old

The recommended vancomycin dose is 10 mg/kg orally every 6 hours for 10 days. The maximum daily dose should not exceed 2 g.

Treatment duration with vancomycin may need to be tailored to the clinical course of individual patients. Whenever possible the antibacterial suspected to have caused CDI should be discontinued. Adequate replacement of fluid and electrolytes should be ensured.

Monitoring of vancomycin serum concentrations

The frequency of therapeutic drug monitoring (TDM) needs to be individualized based on the clinical situation and response to treatment. While a daily sampling may be required in some hemodynamically unstable patients, at least once weekly sampling is needed in stable patients showing a treatment response. In patients with normal renal function, the serum concentration of vancomycin should be monitored on the second day of treatment immediately prior to the next dose.

In patients on intermittent hemodialysis, vancomycin levels should be usually obtained before the start of the hemodialysis session.

After oral administration, monitoring vancomycin serum concentrations in patients with inflammatory intestinal disorders should be performed.

Therapeutic trough (minimum) vancomycin blood levels should normally be 10-20 mg/l, depending on the site of infection and susceptibility of the pathogen.

Trough values of 15-20 mg/l are usually recommended by clinical laboratories to better cover susceptible pathogens with MIC (minimum inhibitory concentration) ≥ 1 mg/L.

Model-based methods may be useful in the prediction of individual dose requirements to reach an adequate AUC. The model-based approach can be used both in calculating the personalized starting dose and for dose adjustments based on TDM results.

Method of administration

Intravenous administration

Intravenous vancomycin is usually administered as an intermittent infusion and the dosing recommendations presented in this section for the intravenous route correspond to this type of administration.

Adequately diluted (at least 100 ml per 500 mg or at least 200 ml per 1000 mg) vancomycin shall only be administered as slow intravenous infusion of at least one hour duration or at a maximum rate of 10 mg/min (whichever is longer).

Patients whose fluid intake must be limited can also receive a solution of 500 mg/50 ml or 1000 mg/100 ml, although the risk of infusion-related undesirable effects can be increased with these higher concentrations.

Continuous vancomycin infusion may be considered in patients with unstable vancomycin clearance.

Oral use

The contents of vials for parenteral administration may be used.

Each dose can be reconstituted in 30 ml of water and given to the patient to drink, as well as through a nasogastric tube.

Common sweetener syrups can be added to the solution to improve taste during application.

4.3. Contraindications

VANKOPOL is contraindicated in patients with known hypersensitivity to vancomycin.

Vancomycin should not be administered intramuscularly due to the risk of necrosis at the site of administration

4.4. Special warnings and precautions for use

Hypersensitivity reactions:

Serious and occasionally fatal hypersensitivity reactions are possible (see sections 4.3 and 4.8). In case of hypersensitivity reactions, treatment with vancomycin must be discontinued immediately and the adequate emergency measures must be initiated.

In patients receiving vancomycin over a long-term period or concurrently with other medications which may cause neutropenia or agranulocytosis, the leukocyte count should be monitored at regular intervals. All patients receiving vancomycin should have periodic hematologic studies, urine analysis, liver and renal function tests.

Vancomycin should be used with caution in patients with allergic reactions to teicoplanin, since cross hypersensitivity, including fatal anaphylactic shock, may occur.

Spectrum of antibacterial activity

Vancomycin has a spectrum of antibacterial activity limited to Gram-positive organisms. It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a high suspicion that the most likely pathogen(s) would be suitable for treatment with vancomycin.

The rational use of vancomycin should take into account the bacterial spectrum of activity, the safety profile and the suitability of standard antibacterial therapy to treat the individual patient.

Ototoxicity

Ototoxicity, which may be transitory or permanent has been reported in patients with prior deafness, who have received excessive intravenous doses, or who receive concomitant treatment with another ototoxic active substance such as an aminoglycoside. Vancomycin should also be avoided in patients with previous hearing loss. Deafness may be preceded by

tinnitus. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment. To reduce the risk of ototoxicity, blood levels should be determined periodically and periodic testing of auditory function is recommended.

The elderly are particularly susceptible to auditory damage. Monitoring of vestibular and auditory function in the elderly should be carried out during and after treatment. Concurrent or sequential use of other ototoxic substances should be avoided.

Infusion-related reactions

Rapid bolus administration (i.e. over several minutes) may be associated with exaggerated hypotension (including shock and, rarely, cardiac arrest), histamine like responses and maculopapular or erythematous rash (“red man's syndrome” or “red neck syndrome”). Vancomycin should be infused slowly in a dilute solution (2.5 to 5.0 mg/ml) at a rate no greater than 10 mg/min and over a period not less than 60 minutes to avoid rapid infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions.

The frequency of infusion-related reactions (hypotension, flushing, erythema, urticaria and pruritus) increases with the concomitant administration of anesthetic agents. (See. Section 4.5) This may be reduced by administering vancomycin by infusion over at least 60 minutes, before anesthetic induction.

Severe bullous reactions

Stevens-Johnson syndrome (SJS) has been reported with the use of vancomycin. (See. Section 4.8). If symptoms or signs of SJS (e.g. progressive skin rash often with blisters or mucosal lesions) are present, vancomycin treatment should be discontinued immediately and a dermatologist should be consulted.

Administration site related reactions

Pain and thrombophlebitis may occur in many patients receiving intravenous vancomycin and are occasionally severe. The frequency and severity of thrombophlebitis can be minimized by administering the medicinal product slowly as a dilute solution (see section 4.2) and by changing the sites of infusion regularly.

The efficacy and safety of vancomycin has not been established for the intrathecal, intralumbar and intraventricular routes of administration.

Nephrotoxicity:

Vancomycin should be used with care in patients with renal insufficiency, including anuria, as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations. The risk of toxicity is increased by high blood concentrations or prolonged therapy.

Regular monitoring of the blood levels of vancomycin is indicated in high dose therapy and long-term use, particularly in patients with renal dysfunction or impaired faculty of hearing as well as in concurrent administration of nephrotoxic or ototoxic substances.

Pediatric population

The current intravenous dosing recommendations for the pediatric population, in particular for children below 12 years of age, may lead to sub-therapeutic vancomycin levels in a substantial

number of children. However, the safety of increased vancomycin dosing has not been properly assessed and higher doses than 60 mg/kg/day cannot be generally recommended.

Vancomycin should be used with particular care in premature neonates and young infants, because of their renal immaturity and the possible increase in the serum concentration of vancomycin. The blood concentrations of vancomycin should therefore be monitored carefully in these children. Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing in children. Similarly, concomitant use with nephrotoxic agents such as aminoglycoside antibiotics, NSAIDs (e.g., ibuprofen for closure of patent ductus arteriosus) or amphotericin B is associated with an increased risk of nephrotoxicity (see section 4.5) and therefore more frequent monitoring of vancomycin serum levels and renal function is indicated.

Use in elderly

The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted (see section 4.2).

Drug interactions with anesthetic agents

Anesthetic induced myocardial depression may be enhanced by vancomycin. During anesthesia, doses must be well diluted and administered slowly with close cardiac monitoring. Position changes should be delayed until the infusion is completed to allow for postural adjustment (see section 4.5).

Pseudomembranous enterocolitis

In case of severe persistent diarrhea the possibility of pseudomembranous enterocolitis that might be life-threatening has to be taken into account (see section 4.8). Anti-diarrheic medicinal products must not be given.

Superinfection

Prolonged use of vancomycin may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Oral administration:

Intravenous administration of vancomycin is not effective for the treatment of *Clostridium difficile* infection. Vancomycin should be administered orally for this indication. Testing for *Clostridium difficile* colonization or toxin is not recommended in children younger than 1 year due to high rate of asymptomatic colonization unless severe diarrhea is present in infants with risk factors for stasis such as Hirschsprung disease, operated anal atresia or other severe motility disorders. Alternative aetiologies should always be sought and *Clostridium difficile* enterocolitis be proven.

Potential for Systemic Absorption

Absorption may be enhanced in patients with inflammatory disorders of the intestinal mucosa or with *Clostridium difficile* induced pseudomembranous colitis. These patients may be at risk

for the development of adverse reactions, especially if there is a concomitant renal impairment. The greater the renal impairment, the greater the risk of developing the adverse reactions associated with the parenteral administration of vancomycin. Monitoring of serum vancomycin concentrations of patients with inflammatory disorders of the intestinal mucosa should be performed.

Nephrotoxicity:

Serial monitoring of renal function should be performed when treating patients with underlying renal dysfunction or patients receiving concomitant therapy with an aminoglycoside or other nephrotoxic drugs.

Ototoxicity:

Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity in patients with an underlying hearing loss, or who are receiving concomitant therapy with an ototoxic agent such as an aminoglycoside.

Drug interactions with anti-motility agents and proton pump inhibitors:

Anti-motility agents should be avoided and proton pump inhibitor use should be reconsidered.

Development of Drug-Resistant Bacteria:

Oral vancomycin use increases the chance of vancomycin-resistant Enterococci populations in the gastrointestinal tract. As a consequence, prudent use of oral vancomycin is advised.

4.5. Interaction with other medicinal products and other forms of interaction

Concurrent administration of vancomycin and anesthetic agents has been associated with erythema, histamine like flushing and anaphylactoid reactions (See section 4.4).

The incidence of infusion-related events was reported to be increased in concurrent use with anesthetic agents. Infusion-related events can be minimized by infusion of vancomycin 60 min prior to anesthetic induction. When administered during anesthesia, the dose should be diluted to 5 mg / ml or less and administered slowly with strict cardiac monitoring. Position changes should be postponed until the infusion has been completed and allowed postural regulation.

Concomitant or consecutive use of systemic or topical other ototoxic or nephrotoxic drugs such as amphotericin B, aminoglycosides, bacitracin, polymyxin B, cholistin, viomycin, cisplatin, loop diuretics (furosemide, ethacrynic acid, etc.) and NSAIDs may increase the toxicity of vancomycin and if it is necessary to administer these drugs, they should be used with care and appropriately.

Oral administration: In view of local guidelines for Clostridium difficile infections, the discontinuation of proton pump inhibitors and anti-motility agents should be considered.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: C

Women with childbearing potential/Contraception

There is no adequate experience with the use of VANKOPOL in women with childbearing potential.

Pregnancy

There is no adequate experience with the use of VANKOPOL in pregnant women.

Studies on animals are insufficient in terms of effects on pregnancy / and-or / embryonal / fetal development / and-or / birth / and-or postnatal development (see section 5.3). Potential risk for human is unknown.

Teratology studies have been performed at 5 times the human dose in rats and 3 times the human dose in rabbits, and have revealed no evidence of harm to the foetus due to vancomycin. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin hydrochloride on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections. Vancomycin hydrochloride was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to vancomycin was noted. One infant, whose mother received vancomycin in the third trimester, experienced conductive hearing loss that was not attributable to vancomycin. Because vancomycin was administered only in the second and third trimesters, it is not known whether it causes fetal harm. Vancomycin should be given in pregnancy only if clearly needed and blood levels should be monitored carefully to minimize the risk of fetal toxicity. It has been reported, however, that pregnant patients may require significantly increased doses of vancomycin to achieve therapeutic serum concentrations.

Lactation

Vancomycin Hydrochloride is excreted in breast milk. Caution should be exercised when vancomycin is administered to breastfeeding women. It is unlikely that a breast-fed infant receives too much vancomycin from the gastro-intestinal tract.

Reproduction/Fertility

No adequate data is available on the effect on reproduction.

4.7. Effects on ability to drive and use machines

It has no effect on the ability to drive and use machines.

4.8. Undesirable effects

Summary of the safety profile

The most common adverse reactions are phlebitis, pseudo-allergic reactions and flushing of the upper body (Red Man Syndrome - RMS) in connection with too rapid intravenous infusion of vancomycin.

The absorption of vancomycin from the gastrointestinal tract is negligible. However, in severe inflammation of the intestinal mucosa, especially in combination with renal insufficiency, adverse reactions that occur when vancomycin is administered parenterally may appear.

Tabulated List of Adverse Reactions

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The adverse reactions listed below are defined using MedDRA system organ class:

Very common ($\geq 1/10$), Common ($\geq 1/100$; $< 1/10$), Uncommon ($\geq 1/1000$; $< 1/100$), Rare ($\geq 1/10,000$; $< 1/1000$), Very rare ($< 1/10,000$), Not known (cannot be estimated from the available data)

System Organ Class	
Frequency	Adverse Reaction
Blood and lymphatic system disorders	
Rare	Reversible neutropenia, agranulocytosis, eosinophilia, thrombocytopenia, pancytopenia.
Immune system disorders	
Rare	Anaphylactic reactions, hypersensitivity reactions
Ear and Labyrinth Disorders	
Uncommon:	Transient or permanent loss of hearing
Rare	Vertigo, tinnitus, dizziness
Cardiac disorders	
Very rare:	Cardiac arrest
Vascular disorders	
Common	Decrease in blood pressure
Rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, stridor
Gastrointestinal disorders	
Rare	Nausea
Very rare:	Pseudomembranous enterocolitis
Not known	Vomiting, diarrhea
Skin and subcutaneous tissue disorders	
Common	Flushing of the upper body ("Red Man Syndrome"), exanthema and mucosal inflammation, pruritus, urticaria
Very rare:	Exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome, linear IgA bullous dermatosis
Not known	Eosinophilia and systemic symptoms (DRESS syndrome), Acute Generalized Exanthematous Pustulosis (AGEP)
Renal and urinary disorders	
Common	Renal insufficiency manifested primarily by increased serum creatinine and serum urea
Rare	Interstitial nephritis, acute renal failure

Not known	Acute tubular necrosis
General disorders and administration site conditions	
Common	Phlebitis, redness of the upper body and face.
Rare	Drug fever, shivering, pain and muscle spasm of the chest and back muscles

Description of selected adverse reactions

Reversible neutropenia usually starting one week or more after onset of intravenous therapy or after total dose of more than 25 g.

During or shortly after rapid infusion anaphylactic/anaphylactoid reactions including wheezing may occur. The reactions abate when administration is stopped, generally between 20 minutes and 2 hours. Vancomycin should be infused slowly. (See sections 4.2 and 4.4) Necrosis may occur after intramuscular injection.

Tinnitus, possibly preceding onset of deafness, should be regarded as an indication to discontinue treatment.

Ototoxicity has primarily been reported in patients given high doses, or in those on concomitant treatment with other ototoxic medicinal product like aminoglycoside, or in those who had a pre-existing reduction in kidney function or hearing.

If a bullous disorder is suspected, the drug should be discontinued and specialized dermatological assessment should be carried out.

Pediatric population

The safety profile is generally consistent among children and adult patients. Nephrotoxicity has been described in children, usually in association with other nephrotoxic agents such as aminoglycosides.

4.9. Overdose

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed from the blood by hemodialysis or peritoneal dialysis. Haemoperfusion with Amberlite resin XAD-4 has been reported to be of limited benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group: Glycopeptide antibacterials

ATC Code: J01 XA01 for intravenous use, A07 AA09 for oral use

Mechanism of action

Vancomycin is a tricyclic glycopeptide antibiotic that inhibits the synthesis of the cell wall in sensitive bacteria by binding with high affinity to the D-alanyl-D-alanine terminus of cell wall precursor units.

The drug is slowly bactericidal for dividing microorganisms. In addition, it impairs the permeability of the bacterial cell membrane and RNA synthesis.

Pharmacokinetic/ Pharmacodynamic relationship

Vancomycin displays concentration-independent activity with the area under the concentration curve (AUC) divided by the minimum inhibitory concentration (MIC) of the target organism as the primary predictive parameter for efficacy. On basis of in vitro, animal and limited human data, an AUC/MIC ratio of 400 has been established as a PK/PD target to achieve clinical effectiveness with vancomycin. To achieve this target when MICs are ≥ 1.0 mg/l, dosing in the upper range and high trough serum concentrations (15-20 mg/l) are required.

Mechanism of resistance

Acquired resistance to glycopeptides is most common in enterococci and is based on acquisition of various van gene complexes which modifies the D-alanyl-D-alanine target to D-alanyl-D-lactate or D-alanyl-D-serine which bind vancomycin poorly. In some countries, increasing cases of resistance are observed particularly in enterococci; multiresistant strains of *Enterococcus faecium* are especially alarming.

Van genes have rarely been found in *Staphylococcus aureus*, where changes in cell wall structure result in intermediate susceptibility, which is most commonly heterogeneous. Also, methicillin-resistant staphylococcus strains (MRSA) with reduced susceptibility for vancomycin were reported. The reduced susceptibility or resistance to vancomycin in *Staphylococcus* is not well understood. Several genetic elements and multiple mutations are required.

There is no cross-resistance between vancomycin and other classes of antibiotics. Cross-resistance with other glycopeptide antibiotics, such as teicoplanin, does occur. Secondary development of resistance during therapy is rare.

Synergism:

The combination of vancomycin with an aminoglycoside antibiotic has a synergistic effect against many strains of *Staphylococcus aureus*, non-enterococcal group D-streptococci, enterococci and streptococci of the Viridans group.

The combination of vancomycin with a cephalosporin has a synergistic effect against some oxacillin-resistant *Staphylococcus epidermidis* strains, and the combination of vancomycin with rifampicin has a synergistic effect against *Staphylococcus epidermidis* and a partial synergistic effect against some *Staphylococcus aureus* strains. As vancomycin in combination with a cephalosporin may also have an antagonistic effect against some *Staphylococcus epidermidis* strains and in combination with rifampicin against some *Staphylococcus aureus* strains, preceding synergism testing is useful.

Specimens for bacterial cultures should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to vancomycin.

Susceptibility testing breakpoints

Vancomycin is active against gram-positive bacteria, such as staphylococci, streptococci, enterococci, pneumococci, and clostridia. Gram-negative bacteria are resistant.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. This information only provides approximate guidance on the chance whether micro-organisms are susceptible to vancomycin.

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

	Susceptible	Resistant
<u><i>Staphylococcus aureus</i></u> ¹	≤ 2 mg/L	> 2 mg/L
<u>Coagulase-negative staphylococci</u> ¹	≤4 mg/L	>4 mg/L
<u><i>Enterococcus spp.</i></u>	≤4 mg/L	>4 mg/L
<u><i>Streptococcus grup A, B, C and G</i></u>	≤2 mg/L	>2 mg/L
<u><i>Streptococcus pneumoniae</i></u>	≤2 mg/L	>2 mg/L
<u>Gram-positive anaerobies</u>	≤2 mg/L	>2 mg/L

¹S. aureus with vancomycin MIC values of 2 mg/L are on the border of the wild type distribution and there may be an impaired clinical response.

Commonly susceptible species
Gram positive <i>Enterococcus faecalis</i> <i>Staphylococcus aureus</i> <i>Methicillin-resistant Staphylococcus aureus</i> <i>Coagulase-negative Staphylococci</i> <i>Streptococcus spp.</i> <i>Streptococcus pneumoniae</i> <i>Enterococcus spp.</i> <i>Staphylococcus spp.</i>
Anaerobic species <i>Clostridium spp. except Clostridium innocuum</i> <i>Eubacterium spp.</i>

<i>Peptostreptococcus spp</i>
Species for which acquired resistance may be a problem
<i>Enterococcus faecium</i>
Inherently resistant
All gram negative bacteria
Gram positive aerobic species <i>Erysipelothrix rhusiopathiae</i> , <i>Heterofermentative Lactobacillus</i> , <i>Leuconostoc spp</i> <i>Pediococcus spp.</i>
Anaerobic species <i>Clostridium innocuum</i>
The emergence of resistance towards vancomycin differs from one hospital to another and a local microbiological laboratory should therefore be contacted for relevant local information

5.2. Pharmacokinetic properties

Absorption

Vancomycin is administered intravenously for the treatment of systemic infections.

In the case of patients with normal renal function, intravenous infusion of multiple doses of 1000 mg vancomycin (15 mg/kg) for 60 minutes produces approximate average plasma concentrations of 50-60 mg/L, 20-25 mg/L and 5-10 mg/L, immediately, 2 hours and 11 hours after completing the infusion, respectively. The plasma levels obtained after multiple doses are similar to those achieved after a single dose.

Vancomycin is not usually absorbed into the blood after oral administration. However, absorption may occur after oral administration in patients with (pseudomembranous) colitis. This may lead to vancomycin accumulation in patients with co-existing renal impairment.

Distribution

The volume of distribution is about 60 L/1.73 m² body surface. At serum concentrations of vancomycin of 10 mg/l to 100 mg/l, the binding of the drug to plasma proteins is approximately 30-55%, measured by ultra-filtration.

Vancomycin diffuses readily across the placenta and is distributed into cord blood. In non-inflamed meninges, vancomycin passes the blood-brain barrier only to a low extent.

Biotransformation

There is very little metabolism of the drug. After parenteral administration it is excreted almost completely as microbiologically active substance (approx. 75-90% within 24 hours) through glomerular filtration via the kidneys.

Elimination:

The elimination half-life of vancomycin is 4 to 6 hours in patients with normal renal function and 2.2-3 hours in children. Plasma clearance is about 0.058 L/kg/h and kidney clearance about 0.048 L/kg/h. In the first 24 hours, approximately 80% of an administered dose of vancomycin is excreted in the urine through glomerular filtration. Renal dysfunction delays the excretion of vancomycin. In anephric patients, the mean half-life is 7.5 days. Due to ototoxicity of vancomycin therapy-adjuvant monitoring of the plasma concentrations is indicated in such cases.

Biliary excretion is insignificant (less than 5% of a dose).

Although the vancomycin is not eliminated efficiently by hemodialysis or peritoneal dialysis, there have been reports of an increase in vancomycin clearance with haemoperfusion and hemofiltration.

After oral administration, only a fraction of the administered dose is recovered in the urine. In contrast, high concentrations of vancomycin are found in the faeces (>3100 mg/kg with doses of 2 g/day).

Linearity / Non-linearity

Vancomycin concentration generally increases proportionally with increasing dose. Plasma concentrations during multiple dose administration are similar to those after the administration of a single dose.

Special populations:

Renal impairment

Vancomycin is primarily cleared by glomerular filtration. In patients with impaired renal function the terminal elimination half- life of vancomycin is prolonged and the total body clearance is reduced. Subsequently, optimal dose should be calculated in line with dosing recommendations provided in section 4.2.

Hepatic impairment:

No dose adjustment is required in patient with hepatic failure.

Pregnant women:

Significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant women (see Section 4.6).

Obese patients:

Vancomycin distribution may be altered in overweight patients due to increases in volume of distribution, in renal clearance and possible changes in plasma protein binding. In these subpopulations vancomycin serum concentration was found higher than expected in male healthy adults (see section 4.2).

Pediatric population

Vancomycin PK (pharmacokinetics) has shown wide inter-individual variability in preterm and term neonates. In neonates, after intravenous administration, vancomycin volume of distribution varies between 0.38 and 0.97 L/kg, similar to adult values, while clearance varies between 0.63 and 1.4 ml/kg/min. Half-life varies between 3.5 and 10 h and is longer than in adults, reflecting the usual lower values for clearance in the neonate.

In infants and older children, the volume of distribution ranges between 0.26-1.05 L/kg while clearance varies between 0.33-1.87 ml/kg/min.

5.3. Preclinical safety data

No long-term studies in animals have been performed to evaluate the carcinogenic potential. Vancomycin was not mutagenic in laboratory tests. No descriptive fertility study was conducted.

6. PHARMACEUTICAL PROPERTIES

6.1. List of Excipients

None.

Vials contain vancomycin hydrochloride only.

6.2. Incompatibilities

Vancomycin solution has a low pH that may cause chemical or physical instability when it is mixed with other compounds. Mixing with alkaline solutions should be avoided.

Mixtures of vancomycin and beta-lactam antibiotic solutions were found to be physically unstable. As the concentration of vancomycin increases, the probability of collapse increases. It is advisable to clean the intravenous sets between the use of these antibiotics. It is also recommended to dilute vancomycin solutions to 5 mg / l or less.

After simultaneous intravitreal injection of vancomycin and ceftazidime, a precipitation was reported. The precipitates were gradually resolved by complete cleaning of the vitreous cavity for two months and improvement of visual acuity.

6.3. Shelf-life

24 months

Shake/swirl until product is completely dissolved during reconstitution.

In addition, product reconstituted with water for injection is physically and chemically stable at 25°C for 24 hours and at 2-8°C for 96 hours when diluted with 0.9% sodium chloride and 5% dextrose solutions.

6.4. Special precautions for storage

Unopened vial should be stored at room temperature below 25°C.

6.5. Nature and contents of container

VANKOPOL is available in colorless glass vial. Vials are covered with bromobutyl rubber stopper and plastic cap.

6.6. Special precautions for disposal of waste materials derived from the medicinal product and other handling

Any unused medicinal product or waste material should be disposed of in accordance with the local regulations.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

2018/601

9. DATE OF FIRST LICENSE/RENEWAL OF THE LICENSE

Date of first license: 30.10.2018

Date of renewal of the license:

10. DATE OF REVISION OF THE TEXT

04.12.2019