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# Vancomycin

# Vancosan

1 g Powder for Injection (I.V.)
Antibacterial (Glycopeptide)

℞

**FORMULATION**:
Each vial contains:
Vancomycin hydrochloride 1.03 g
equivalent to Vancomycin ..... 1 g

**PRODUCT DESCRIPTION:**
White, almost white, or tan to brown, free-flowing powder, odorless, and having a bitter taste.

**PHARMACOLOGICAL PROPERTIES:**
**Pharmacodynamics**
Pharmacotherapeutic group: glycopeptide antibacterials
*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.
**Pharmacokinetics**
*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 1 g of 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 $m^2$ 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 a 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 is 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 the 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 Vancomycin is not eliminated efficiently by hemodialysis or peritoneal dialysis, there have been reports of an increase in Vancomycin clearance with hemoperfusion and hemofiltration.

**INDICATIONS:**
Intravenous administration
Vancomycin is indicated in all age groups for the treatment of the following infections:
- Complicated Skin and Soft Tissue Infections (cSSTI)
- Bone and Joint Infections
- Community-Acquired Pneumonia (CAP)
- Hospital-Acquired Pneumonia (HAP), including Ventilator-Associated Pneumonia (VAP)
- Infective Endocarditis

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

**DOSAGE AND ADMINISTRATION:**
Posology
Where appropriate, Vancomycin should 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 intervals of administration.
**Patients aged 12 years and older**
The recommended dose is 15 to 20 mg/kg of body weight every 8 to 12 hours(not to exceed 2 g per dose).
In seriously ill patients, a loading dose of 25-30 mg/kg of body weight can be used to facilitate rapid attainment of the target through 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:
Duration of treatment
Suggested treatment duration is shown in the table below. In any case, the duration of treatment should be tailored to the type and severity of infection and the individual clinical response.

| PMA (weeks) | Dose (mg/kg) | Dose (mg/kg) |
|---|---|---|
| <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 before induction of anesthesia. Depending on the duration of surgery, a second Vancomycin dose may be required.

| Indication | Treatment duration |
|---|---|
| Complicated skin and soft tissue infections | |
| - Non necrotizing | 7 to 14 days |
| - Necrotizing | 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, a patient has clinically improved, and the 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 are based on valve type and organism.
Special populations
*Elderly*
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 trough levels rather than to a scheduled dosing regimen, particularly in patients with severe renal impairment or those who undergo renal replacement therapy (RRT) due to the many varying factors that may affect Vancomycin levels in them.
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, the use of high-flux membranes and continuous renal replacement therapy (CRRT) increases Vancomycin clearance and generally requires replacement dosing (usually after the hemodialysis session in case of intermittent hemodialysis).
*Adults*
Dose adjustments in adult patients could be based on glomerular filtration rate estimated (eGFR) by the following formula:
Men: [Weight (kg) x 140 - age (years)]/ 72 x 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 the glomerular filtration rate estimated (eGFR) by the revised Schwartz formula:
eGFR (mL/min/1.73 $m^2$) = (height cm x 0.413)/ serum creatinine (mg/dL)
eGFR (mL/min/1.73 $m^2$) = (height cm x 36.2)/serum creatinine (µmol/L)
For neonates and infants below 1 year of age, expert advice should be sought as the revised Schwartz formula does not apply to them.
Orientative dosing recommendations for the pediatric population are shown in the table below and follow the same principles as in adult patients.

| GFR (mL/min/1.73 $m^2$) | IV dose | Frequency |
|---|---|---|
| 50-30 | 15 mg/kg | 12 hourly |
| 29-10 | 15 mg/kg | 24 hourly |
| < 10 | | Re-dose based on levels* |
| Intermittent hemodialysis | 10-15 mg/kg | |
| Peritoneal dialysis | | |
| Continuous renal replacement therapy | 15 mg/kg | Re-dose based on levels* |

*The appropriate timing and amount of subsequent doses largely depend on the modality of RRT and should be based on serum Vancomycin levels obtained before dosing and on residual renal function. Depending on the clinical situation, consideration could be given to withholding the next dose while awaiting the results of Vancomycin levels.
*Hepatic impairment*
No dose adjustment is needed in patients with hepatic insufficiency.
*Obese patients*
In obese patients, the initial dose should be individually adapted according to total body weight as in non-obese patients.
Or as prescribed by the physician.
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.
Vancomycin shall only be administered as a slow intravenous infusion of at least one-hour duration or at a maximum rate of 10 mg/min (whichever is longer) which is sufficiently diluted (at least 100 mL per 500 mg or at least 200 mL per 1000 mg).
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, e.g., in patients with unstable Vancomycin clearance.

**CONTRAINDICATIONS:**
Hypersensitivity to the active substance.
Vancomycin should not be administered intramuscularly due to the risk of necrosis at the site of administration.

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE:**
Hypersensitivity reactions
Serious and occasionally fatal hypersensitivity reactions are possible. In case of hypersensitivity reactions, treatment with Vancomycin must be discontinued immediately and adequate emergency measures must be initiated.
In patients receiving Vancomycin over a longer-term period or concurrently with other medications that may cause neutropenia or agranulocytosis, the leukocyte count should be monitored at regular intervals.

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All patients receiving Vancomycin should have periodic haematologic studies, urine analysis, and 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. 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. 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 specialized dermatological assessment be sought.

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 and by changing the sites of infusion regularly.
The efficacy and safety of Vancomycin have 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 longer-term use, particularly in patients with renal dysfunction or impaired faculty of hearing as well as in concurrent administration of nephrotoxic or ototoxic substances, respectively.

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 and therefore more frequent monitoring of Vancomycin serum levels and renal function is indicated.

Use in the elderly

The natural decrement of glomerular filtration with increasing age may lead to elevated Vancomycin serum concentrations if dosage is not adjusted.

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.

*Pseudomembranous enterocolitis*

In case of severe persistent diarrhea, the possibility of *pseudomembranous enterocolitis* that might be life-threatening has to be taken into account. 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.

**ADVERSE DRUG REACTIONS:**

Summary of the Safety profile

The most common adverse reactions are phlebitis, pseudo-allergic reactions, and flushing of the upper body ("red-neck syndrome") 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 the following MedDRA convention and system organ class database:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

| **System organ class** | |
|---|---|
| **Frequency** | **Adverse drug reaction** |
| **Blood and the lymphatic system disorders:** | |
| Rare | Reversible neutropenia, agranulocytosis, eosinophilia, thrombocytopenia, pancytopenia. |
| **Immune system disorders:** | |
| Rare | Hypersensitivity reactions, anaphylactic 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 | Dyspnea, 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), AGEP (Acute Generalized Exanthematous Pustulosis) |
| **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 drug reactions

Reversible neutropenia usually starts one week or more after the onset of intravenous therapy or after a 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. Necrosis may occur after intramuscular injection.
Tinnitus, possibly preceding the onset of deafness, should be regarded as an indication to discontinue treatment.
Ototoxicity has primarily been reported in patients given high doses, in those on concomitant treatment with other ototoxic medicinal products like aminoglycosides, 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.

**DRUG INTERACTIONS:**

Concomitant administration of Vancomycin and anesthetic agents has been associated with erythema, histamine-like flushing and anaphylactoid reactions.
There have been reports that the frequency of infusion-related events increases with the concomitant administration of anesthetic agents. Infusion-related events may be minimized by the administration of Vancomycin as a 60-minute infusion before anesthetic induction. When administered during anesthesia, doses must be diluted to 5 mg/mL or less and administered slowly with close cardiac monitoring. Position changes should be delayed until the infusion is completed to allow for postural adjustment.
Concurrent or sequential systemic or topical use of other potentially ototoxic or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymixin B, colistin, viomycin, cisplatin, loop diuretics, and NSAIDs may increase the toxicity of Vancomycin and if they need to be given should be used with caution and appropriate monitoring.

**PREGNANCY AND LACTATION:**

Pregnancy

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 fetus 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 complicating intravenous drug abuse. 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 a 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.

Breastfeeding

Vancomycin hydrochloride is excreted in human milk. Caution should be exercised when Vancomycin is administered to a nursing woman. It is unlikely that a nursing infant can absorb a significant amount of Vancomycin from its gastrointestinal tract.

**OVERDOSE AND TREATMENT:**

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

**CAUTION:**

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

**KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.**

**STORAGE CONDITION:**

Store at temperatures not exceeding 30°C.

**AVAILABILITY:**

10 mL USP Type II colorless glass vial, with gray bromobutyl rubber stopper, aluminum cap, and blue plastic flip-off seal (Box of 1's)

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