SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vancomycin Viatris 500 mg

Vancomycin Viatris 1000 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vancomycin 500 mg lyophilized powder for concentrated solution.

Each vial contains 500 mg vancomycin (as hydrochloride), equivalent to 500,000 IU.

When reconstituted with 10 ml of water for injections, the solution contains 50mg/ml vancomycin.

Vancomycin 1000 mg lyophilized powder for concentrated solution.

Each vial contains 1 g vancomycin (as hydrochloride), equivalent to 1,000,000 IU.

When reconstituted with 20 ml of water for injections, the solution contains 50mg/ml vancomycin.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilized powder for concentrated solution for intravenous infusion or for oral solution.

White to almost white or slightly pink or yellow powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Intravenous infusion

Vancomycin hydrochloride is indicated for the treatment of severe or serious infections due to susceptible strains of methicillin - resistant (beta-lactam-resistant) staphylococci.

It is also indicated for administration to penicillin-allergic patients as well patients who have failed to respond to or who cannot receive other drugs including cephalosporins or penicillins and for infections due to vancomycin-susceptible organisms that are resistant to other antimicrobial drugs.

Vancomycin hydrochloride is indicated for first-line therapy when methicillin-resistant staphylococci are suspected but when susceptibility data become available appropriate therapy should be instituted.

Vancomycin hydrochloride is effective in the treatment of staphylococcal endocarditis as well as in other infections due to staphylococci including lower respiratory tract infections septicemia skin and skin - structure infection and bone infections.

Antibiotic therapy is as an adjunct to appropriate surgical measures when staphylococcal infections are purulent and localized.

For endocarditis due to Streptococcus viridans or Streptococcus bovis vancomycin hydrochloride has been shown to be effective in combination with an aminoglycoside.

Vancomycin hydrochloride has been shown to be effective only in combination with an aminoglycoside for endocarditis due to enterococci (eg Enterococcus fecalis).

Vancomycin hydrochloride has been shown to be effective for the treatment of diphtheroid endocareditis. In early-onset prosthetic valve endocarditis caused by Staphylococcus epidermidis or diptheroids vancomycin hydrochloride has been administered successfully in combination with either rifampin an aminoglycoside or combined with both drugs.

Bacteriologic cultures of specimens should be obtained for isolation and identification of causative organisms and determination of susceptibilities to vancomycin hydrochloride.

Oral administration

Vancomycin hydrochloride injection may be given orally for the treatment of antibiotic- associated Pseudomembrannous colitis due to Staphylococcus enterocolitis and Clostridium difficile. Vancomycin hydrochloride is not effective orally when administered for other types of infection.

4.2. Posology and method of administration

Therapeutic indications for intravenous and oral administration are different. Both administration routes could not be commuted.

Intravenous administration

Solution concentrations of no more than 5 mg/ml are recommended. In selected patients in need of fluid restriction, solution concentration up to 10 mg/ml may be used; use of such higher concentrations may increase the risk of infusion-related events (see section 6.6).

Infusions should be given over at least 60 minutes. In adults, if doses exceeding 500 mg are used, a rate of infusion of no more than 10 mg/min is recommended. Infusion-related adverse events are related to both concentration and rate of administration of vancomycin.

The duration of treatment is guided by the severity of the infection and its clinical and bacteriological Progression.

Patients with normal renal and hepatic functions

Adult and adolescents above 12 years of age:

The recommended daily intravenous dose is 2000 mg (2g), divided into doses of 500mg every 6 hours or 1000mg every 12 hours.

For bacterial endocarditis, the generally accepted regimen is 1000 mg of vancomycin intravenously every 12 hours for 4 weeks either alone or in combination with other antibiotics (gentamicin plus rifampin, gentamicin, streptomycin).

Enterococcal endocarditis is treated for 6 weeks with vancomycin in combination with an Aminoglycoside – according to national recommendations.

Children 1 month to 12 years of age:

The recommended intravenous dose is 10mg/kg, every 6 hours.

Infants and newborn:

The recommended initial dose is 15 mg/kg, followed by 10 mg/kg every 12 hours during the first week of life and every 8 hours after that age and up to 1 month of age. Careful monitoring of serum concentration of vancomycin is recommended (see below).

Elderly patients:

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

Obese patients:

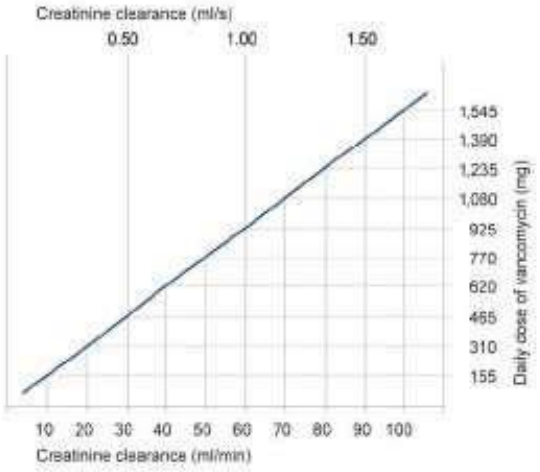
Modification of the usual daily doses may be required.

Patients with impaired hepatic function

There is no evidence that the dose has to be reduced in patients with impaired hepatic function.

Patients with impaired renal function

The dose must be adjusted in patients with impaired renal function and the following nomogram can serve as guidance. Careful monitoring of serum concentration of vancomycin is recommended (see below)



Dosing nomogram for adults with impaired renal function

If the creatine clearance is not available, the following formula may be applied to calculate the creatinine clearance from the patients age, sex and serum creatinine:

$$\text{Men:}\quad \frac{\text{Weight [kg] x (140 - age [years])}}{\text{72 x serum creatinine [mg/100 ml]}}$$

Women: 0.85 x value calculated by the above formula.

Where possible, the creatinine clearance should always be determined.

In patients with mild or moderate renal failure, the starting dose must not be less than 15 mg/kg. In patients with severe renal failure, it is preferable to administer a maintenance dose between 250 mg and 1000 mg at a spacing of several days rather than administer lower daily doses.

Patients with anuria (with practically no renal function) should receive a dose of 15 mg/kg body weight until the therapeutic serum concentration is reached. The maintenance doses are 1.9 mg/kg body weight per 24 hours.

In order to facilitate the procedure, adult patients with strongly impaired renal function may obtain amaintenance dose of 250 - 1000 mg at intervals of several days instead of a daily dose.

Dosage in case of haemodialysis

For patients without any renal function, even under regular hemodialysis, the following dosage is also possible: Saturating dose 1000 mg, maintenance dose 1000 mg every 7 - 10 days.

If polysulfone membranes are used in haemodialysis (high flux dialysis), the half-life of vancomycin is reduced. An additional maintenance dose may be necessary in patients on regular haemodialysis.

Monitoring of vancomycin serum concentrations:
The serum concentration of vancomycin should be monitored at the second day of treatment immediately prior to the next dose, and one hour post infusion. Therapeutic vancomycin blood levels should be between 30 and 40 mg/l (maximum 50 mg/l) one hour after the end of the infusion, the minimum level (short prior to the next administration) between 5 and 10 mg/l.
The concentrations should normally be monitored twice or three times per week.

Oral administration

Treatment of colitis due to C. difficile

Adults: The usual daily dose is 0,5g to 2 g given in 4 divided doses (125 mg to 500 mg per dose) for 7 to 10 days.

Children: The usual daily dose is 40 mg/kg/day given in 4 divided doses, up to a maximum of 250 mg/dose, for 7 to 10 days.

Method of Administration

For intravenous infusion only, and not for intramuscular administration.

Parenterally vancomycin shall only be administered as slow intravenous infusion (not more than 10 mg/min – over at least 60 min) which is sufficiently diluted (at least 500 mg/100ml or at least 1000mg/200 ml).

Patients requiring fluid restriction can receive a solution of 500 mg /50 ml or 1000 mg /100 ml. With these higher concentrations the risk for infusion related side effects can be increased.

Oral administration:

For information about the preparation of the solution, please refer to section 6.6 special precautions for disposal and other handling.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

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 longer-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 haematologic 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 (see section 4.8) 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 anaesthetic agents (see section 4.5). This may be reduced by administering vancomycin by infusion over at least 60 minutes, before anaesthetic induction.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with vancomycin treatment (see section 4.8). Most of these reactions occurred within a few days and up to eight weeks after commencing treatment with vancomycin.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, vancomycin should be withdrawn immediately and an alternative treatment considered. If the patient has developed a SCAR with the use of vancomycin, treatment with vancomycin must not be restarted at any time.

Cardiovascular and cerebrovascular effects

Cases of Kounis syndrome have been reported in patients treated with vancomycin.

Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitivity reaction associated with constriction of the coronary arteries, which may lead to myocardial infarction.

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.

The administration of vancomycin by intraperitoneal injection during continuous ambulatory peritoneal dialysis has been associated with a syndrome of chemical peritonitis.

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 (see sections 4.2 and 4.5).

Eye disorders

Vancomycin is not authorized for intracameral or intravitreal use, including prophylaxis of endophthalmitis.

Hemorrhagic occlusive retinal vasculitis (HORV), including permanent loss of vision, have been observed in individual cases following intracameral or intravitreal use of vancomycin during or after cataract surgery.

Paediatric population

The current intravenous dosing recommendations for the paediatric 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 anaesthetic 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 the 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 anaesthetic agents

Anaesthetic induced myocardial depression may be enhanced by vancomycin. During anaesthesia, 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 diarrhoea the possibility of pseudomembranous enterocolitis that might be life-threatening has to be taken into account (see section 4.8). Anti-diarrhoeic 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 colonisation unless severe diarrhoea 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 minimise 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

Other potentially nephrotoxic or ototoxic medications

Concomitant or sequential administration of vancomycin and other potentially ototoxic or nephrotoxic medicinal products may increase the ototoxicity or nephrotoxicity. Nephrotoxic medicinal products may include iodine-containing contrast media, aminoglycoside antibiotics, platinum-based chemotherapy agents, methotrexate at high doses, piperacilline/tazobactam and some antiviral drugs such as pentamidine, foscarnet, aciclovir, ganciclovir, famciclovir, valaciclovir, valganciclovir, ciclosporin or tacrolimus (see section 4.4). Aminoglycoside antibiotics, platinum-based chemotherapy agents and some diuretics could be ototoxic drugs. The patient should be closely monitored, especially in case of concomitant administration of aminoglycoside antibiotics. The maximum dose of vancomycin will be restricted to 500 mg every 8 hours.

Anaesthetics

It has been reported that the incidence of possible adverse drug reactions (e.g. hypotension, skin flushing, erythema, urticaria, myocardial depression or pruritus) increases when vancomycin is administered concurrently with anaesthetics. To prevent these adverse drug reactions, vancomycin should be administered at least 60 minutes before anaesthetic induction (see section 4.4).

Muscle relaxants

If vancomycin hydrochloride is administered during or immediately after surgery, the effects of the muscle relaxants administered concurrently (in particular succinylcholine), such as neuromuscular blockade may be enhanced or prolonged.

Oral anticoagulants

Concomitant administration of vancomycin and warfarin may increase the effects of the anticoagulants. Numerous cases of increased oral anticoagulants activity have been reported in patients receiving antibiotics. A marked infectious or inflammatory context, age and general condition of the patient appear to be risk factors. Under these circumstances, it is difficult to distinguish between the infectious disease and its treatment in the onset of the INR imbalance. It is recommended to monitor INR frequently during and rapidly after concomitant administration of vancomycin with oral anticoagulants.

Paediatric population

Interaction studies have only been performed in adults.

Special problems of INR imbalance

Numerous cases of increase in the activity of oral anticoagulants have been reported in patients treated with antibiotics. A marked infectious or inflammatory context, the age and the patient's general condition appear as risk factors. Under these circumstances, it would seem difficult to differentiate between the infectious pathology and its treatment in the appearance of the INR imbalance. However, certain antibiotic classes are more deeply involved: particularly fluoroquinolones, macrolides, cyclins, cotrimoxazole and some cephalosporins.

4.6. Fertility, pregnancy and lactation

Pregnancy

The high therapeutic benefit of this molecule justifies that its use may be envisaged, if necessary, during pregnancy, irrespective of the term. Animal data have not demonstrated any teratogenic effect, however the clinical data remain insufficient. In view of the ototoxicity of vancomycin, an evaluation of the auditory function (oto emissions) of the newborn may be performed in case of use during pregnancy.

Lactation

In view of the very low excretion of vancomycin in milk and its low digestive absorption, the use of vancomycin administered by injection or by oral route could be considered during breast-feeding, if necessary

4.7. Effects on ability to drive and use machines

Vancomycin has no or negligible influence 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-neck syndrome") in connection with too rapid intravenous infusion of vancomycin.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) have been reported in association with vancomycin treatment (see section 4.4).

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 reaction**
Blood and the lymphatic system disorders	
Rare	Reversible neutropenia[1], agranulocytosis, eosinophilia, thrombocytopenia, pancytopenia.
Not known	Hemolytic anemia
Hepatobiliary disorders	
Common	Alanine aminotransferase increased, aspartate aminotransferase increased
Immune system disorders:	
Rare	Hypersensitivity reactions, anaphylactic reactions[2]
Ear and labyrinth disorders:	
Uncommon	Transient or permanent loss of hearing[4]
Rare	Vertigo, tinnitus[3], dizziness
Cardiac disorders	
Very rare	Cardiac arrest
Not known	Kounis syndrome
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, Diarrhoea
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, Toxic epidermal necrolysis (TEN), Linear IgA bullous dermatosis
Not known	Eosinophilia and systemic symptoms (DRESS syndrome (drug-induced hypersensitivity 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

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

[2]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.

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

[4]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.

Paediatric 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9. Overdose

In case of overdose, the symptoms include ototoxicity, “red man’s syndrome”, and renal failure with elevation of serum creatinine and urea concentrations.

Measures to be applied in case of overdose

• There is no known specific antidote.

• Symptomatic treatment must be initiated while maintaining renal function.

Vancomycin is poorly removed from the blood by haemodialysis or peritoneal dialysis. Haemofiltration or haemoperfusion with polysulfone resins have been used to reduce serum concentrations of vancomycin.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ANTIBIOTIC ANTIBACTERIAL AGENT OF THE GLYCOPEPTIDE FAMILY (J: anti-infectious), ATC code: J01XA01

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 (see section 4.2).

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; multi-resistant 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.

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Vancomycin and are listed here :

https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Commonly susceptible species
Gram positive
Enterococcus faecalis.
Staphylococcus aureus
Methicillin-resistant *Staphylococcus aureus*
Coagulase negative Staphylococci
Streptococcus spp.
Streptococcus pneumoniae
Enterococcus spp.
Staphylococcus spp.
Anaerobic species
Clostridium spp except *Clostriduim innocuum*
Eubacterium spp.
Peptostreptococcus spp.
Inconstant susceptible species (acquired resistance ≥ 10%)

Enterococcus faecium
Inherently resistant **All Gram negative bacteria** **Gram positive aerobic species** *Erysipelothrix rhusiopathiae* *Heterofermentative Lactobacillus* *Leuconostoc spp.* *Pediococcus spp.* **Anaerobic species** *Clostridium innocuum*
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 1 g 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.

If vancomycin is administered during a peritoneal dialysis intraperitoneally, approximately 30-65% reach the systemic cycle during the first 6 hours. After intraperitoneal administration of 30 mg/kg serum levels of approximately 10 mg/L are reached.

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 haemodialysis or peritoneal dialysis, there have been reports of an increase in vancomycin clearance with haemoperfusion and haemofiltration.

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.

Characteristics in specific groups

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. Posology and method of administration.

Hepatic impairment

Vancomycin pharmacokinetics is not altered in patients with hepatic impairment.

Pregnant Women

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

Overweight 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 were found higher than expected in male healthy adults (see section 4.2).

Paediatric population

Vancomycin PK 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 evidence of genotoxic effect has been found in the standard tests performed.

Long term studies to evaluate the carcinogenic potential of vancomycin have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hydrochloric acid (pH adjustment)

Water for injections

6.2. Incompatibilities

Vancomycin solution has a low pH value. This may lead to chemical or physical instability if mixed with other substances. Therefore, each parenteral solution should be checked visually for precipitations and discolouration prior to use.

Combined treatment

In case of treatment combining vancomycin with other antibiotics/chemotherapy agents, the preparations must be administered separately.

The mixture of vancomycin and beta-lactam antibiotics solutions has been shown to be physically incompatible. The likelihood of precipitation increases with higher concentrations of vancomycin. It is

recommended to thoroughly rinse the infusion lines between the administration of these antibiotics. It is also recommended to dilute the vancomycin solutions to 5 mg/mL or less.

The administration of vancomycin by intravitreal injection is not authorised. Precipitation has been observed following intravitreal injection of vancomycin and ceftazidime using separate syringes and needles for the treatment of endophthalmitis. The precipitate in the vitreous body dissolved completely but slowly over a period of 2 months, during which visual acuity also improved.

6.3. Shelf life

The expiry date of the product is indicated on the label and packaging.

Vancomycin Viatris 500 mg:
Reconstituted solution in water for injections:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C.

Diluted solution using 0.9 % NaCl or 5 % glucose solution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C.

NOTE: The maximum storage time of the reconstituted and diluted solution is 24 hours.

Vancomycin Viatris 1000 mg:
Reconstituted solution in water for injections:
Chemical and physical in-use stability has been demonstrated for 96 hours at 2°C - 8°C.

Diluted solution using 0.9 % NaCl or 5 % glucose solution:
Chemical and physical in-use stability has been demonstrated for 96 hours at 2°C - 8°C.

NOTE: The maximum storage time of the reconstituted and diluted solution is 96 hours.

From a microbiological point of view, the prepared *solution for infusion* should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution / dilution (etc) has taken place in controlled and validated aseptic conditions.

Shelf life of the reconstituted solution for oral use: the reconstituted solution should be used immediately.

6.4. Special precautions for storage

To be stored below 25°C.

For the storage conditions after reconstitution, see section 6.3.

6.5. Nature and contents of container

Neutral type II colourless glass vial, with a bromobutyl rubber stopper sealed with aluminium capsule with plastic tear-off cap.

Pack size: 1 vial.

6.6. Special precautions for disposal and other handling

Preparation of the solution for infusion
The product must be reconstituted and the resulting concentrate must then be diluted prior to use.
Vancomycin 500 mg: dissolve the contents of one vial in 10 ml of water for injections.
For Vancomycin1000 mg: dissolve the contents of one vial in 20 ml of water for injections.
The reconstituted solution should be a clear colourless to slightly yellowish solution, without visible particles.

One ml of reconstituted solution contains 50 mg of vancomycin.

For storage conditions of the reconstituted product see section 6.3.

Suitable diluents for further dilution are water for injections, 5% glucose solution or 0.9% sodium chloride solution.
Different dilution is required depending on method of administration.

- Intermittent infusion:

Vancomycin 500 mg:
Reconstituted solutions containing 500 mg vancomycin must be diluted with at least 100 ml diluent. The desired dose should be administered by intravenous infusion at a rate of no more than 10 mg/min, over at least 60 minutes.
Vancomycin 1000 mg:
Reconstituted solutions containing 1 g vancomycin must be diluted with at least 200 ml diluent. The desired dose should be administered by intravenous infusion at a rate of no more than 10 mg/min, over at least 60 minutes.

- Continuous infusion:

This should be used only if treatment with an intermittent infusion is not possible.
1 g or 2 g of vancomycin, corresponding to 2 to 4 vials of reconstituted solution, may be added to a sufficiently large volume of the above suitable diluent to permit the desired daily dose to be infused over twenty-four hours.
For storage conditions of the diluted product see section 6.3.

Before administration, the reconstituted and diluted solutions should be inspected visually for particulate matter and discoloration. Only clear and colourless to pale yellow solution free from particles should be used.

Preparation of the oral solution

After initial reconstitution of the vial, the selected dose may be diluted in 30 ml of water and given to the patient to drink or the diluted material may be administered by a nasogastric tube.

Disposal

Vials are for single use only. Unused medicinal products must be discarded.

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

7. MARKETING AUTHORISATION HOLDER:

Dexcel Ltd.

1 Dexcel Street, Or Akiva 3060000, Israel

8. MARKETING AUTHORISATION NUMBER(S):

VANCOMYCIN VIATRIS 500 MG: 123-63-30297-00

VANCOMYCIN VIATRIS 1000 MG: 123-64-30298-00

Revised in March 2026 according to MOH guidelines.