1. NAME OF THE MEDICINAL PRODUCT

Vancomycin - Fresenius 500 mg Powder for concentrated solution.

Vancomycin - Fresenius 1000 mg Powder for concentrated solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Vancomycin - Fresenius 1000 - Each vial contains 1000 mg vancomycin (as vancomycin hydrochloride equivalent to 1,000,000 IU).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrated solution.
Infusion, oral.
A white to cream coloured porous cake'
After reconstitution a solution is obtained with a pH of approximately 3.

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 - stucture 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.
Vancomycin is ineffective in these diseases if given parenterally

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

4.2 Posology and method of administration

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.

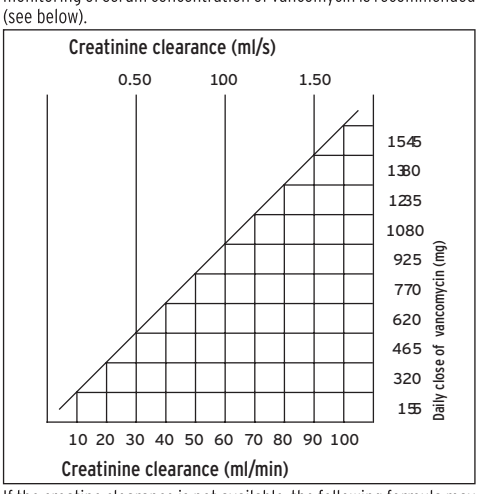
Infants and newborn:
The recommended initial dose is 15 mg/kg, followed by 10 mg/kg every 12 hours during the first week of life and every 8 hours after that age and up to 1 month of age. Careful monitoring of serum concentration of vancomycin is recommended (see below).

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).



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:

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

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 a maintenance 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

Oral administration:
The contents of one 500 mg / 1000 mg vial can be dissolved in 30 ml / 60 ml of water and given to the patient to drink in parts or be administered by gastric tube. Flavouring can be added to this preparation.

4.3 Contraindications

Vancomycin is contraindicated in patients with known hypersensitivity to this drug.

4.4 Special warnings and precautions for use

Warnings
Rapid bolus administration (e.g., over several minutes) may be associated with exaggerated hypotension, including shock, and, rarely, cardiac arrest. Vancomycin should be infused in a dilute solution over a period of not less than 60 minutes to avoid rapid infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions (see ‚Posology and method of administration' and ‚Undesirable effects' sections).
Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of oral vancomycin and, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of vancomycin. The risk is greater in patients with renal impairment. It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly.
Due to its potential ototoxicity and nephrotoxicity, vancomycin should be used with care in patients with renal insufficiency and the dose should be reduced according to the degree of renal impairment. The risk of toxicity is appreciably increased by high blood concentrations or prolonged therapy. Blood levels should be monitored and renal function tests should be performed regularly.
Vancomycin should also be avoided in patients with previous hearing loss. If it is used in such patients, the dose should be regulated, if possible, by periodic determination of the drug level in the blood. Deafness may be preceded by tinnitus.
The elderly are more susceptible to auditory damage. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment.
Vancomycin should be administered with caution in patients allergic to teicoplanin, since allergic cross reactions between vancomycin and teicoplanin have been reported.

Usage in paediatrics: In premature neonates and young infants, it may be appropriate to confirm desired vancomycin serum concentrations. Concomitant administration of vancomycin and anaesthetic agents has been associated with erythema and histamine-like flushing in children.

Usage 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 ‚Posology and method of administration').

Precautions
Clinically significant serum concentrations have been reported in some patients being treated for active C. difficile-induced pseudomembranous colitis after multiple oral doses of vancomycin. Therefore, monitoring of serum concentrations may be appropriate in these patients.
Patients with borderline renal function and individuals over the age of 60 should be given serial tests of auditory function and of vancomycin blood levels. All patients receiving the drug should have periodic haematological studies, urine analysis and renal function tests.
Vancomycin is very irritating to tissue, and causes injection site necrosis when injected intramuscularly; it must be infused intravenously. Injection site pain and thrombophlebitis occur in many patients receiving vancomycin and are occasionally severe.
The frequency and severity of thrombophlebitis can be minimised by administering the drug slowly as a dilute solution (2.5 to 5.0 g/l) and by rotating the sites of infusion.
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. In rare instances, there have been reports of pseudomembranous colitis, due to C. difficile, developing in patients who received intravenous vancomycin.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of vancomycin and anaesthetic 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 anaesthetic agents. Infusion-related events may be mimmised by the administration of vancomycin as a 60-minute infusion prior to anaesthetic induction.
Concurrent or sequential systemic or topical use of other potentially neurotoxic or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymixin B, colistin, viomycin or cisplatin, when indicated, requires careful monitoring.

4.6 Pregnancy and lactation

Usage in 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 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 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 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 foetal harm. Vancomycin should be given in pregnancy only if clearly needed and blood levels should be monitored carefully to minimise the risk of foetal toxicity. It has been reported, however, that pregnant patients may require significantly increased doses of vancomycin to achieve therapeutic serum concentrations.

Usage in nursing mothers: 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 gastro-intestinal tract.

4.7 Effects on ability to drive and use machines
Not applicable.

4.8 Undesirable effects
Infusion-related events: During or soon after rapid infusion of vancomycin, patients may develop anaphylactoid reactions including hypotension, wheezing, dyspnoea, urticaria or pruritus. Rapid infusion may also cause flushing of the upper-body ('red-neck' syndrome) or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours. In animal studies, hypotension and bradycardia occurred in animals given large doses of vancomycin at high concentrations and rates. Such events are infrequent if vancomycin is given by slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when vancomycin was administered at a rate of 10mg/min or less.
Rapid bolus injection may give hypotension, bradycardia, cardiogenic shock and rarely cardiac arrest.

Nephrotoxicity: Rarely, renal failure, principally manifested by increased serum creatinine or blood urea concentrations, have been observed, especially in patients given large doses of intravenously administered vancomycin. Rare cases of interstitial nephritis have been reported. Most occurred in patients who were given aminoglycosides concomitantly or who had pre-existing kidney dysfunction. When vancomycin was discontinued, azotaemia resolved in most patients.

Ototoxicity: Hearing loss associated with intravenously administered vancomycin has been reported. Most of these patients had kidney dysfunction, pre-existing hearing loss, or concomitant treatment with an ototoxic drug. Vertigo, dizziness and tinnitus have been reported rarely. Tinnitus, possibly preceding onset of deafness, may occur and should be regarded as an indication to discontinue treatment.

Haematological: Reversible neutropenia, usually starting one week or more after onset of intravenous therapy or after a total dose of more than 25 g. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been reported. Reversible agranulocytosis (less than 500 granulocytes per mm^3) has been reported rarely, although causality has not been established. Eosinophilia has been reported.

Miscellaneous: Phlebitis, hypersensitivity reactions anaphylaxis, nausea, chills, drug fever, rashes (including exfoliative dermatitis) and rare cases of vasculitis. Vancomycin has been associated with the bullous eruption disorders, Stevens-Johnson syndrome, toxic epidermal necrolysis and linear IgA bullous dermatosis. If a bullous disorder is suspected, the drug should be discontinued and specialist dermatological assessment should be carried out.

Immune system disorder: Drug reaction with eosinophilia and systemic symptoms (DRESS Syndrome).

Reporting of suspected adverse reactions
Reporting of 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://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il
Side effects can also be reported to the following email: safety@trima.co.il

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

5.1 Pharmacodynamic properties
ATC Code: J01 XA01 for intravenous use and A07 AA09 for oral use.
Vancomycin is a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis*. The primary mode of action of vancomycin is inhibition of cell-wall synthesis. In addition, vancomycin may alter bacterial cell membrane permeability and RNA synthesis. There is no cross-resistance between vancomycin and other classes of antibiotics.

EUCAST Clinical MIC Breakpoints

EUCAST Clinical MIC (version 6.0, valid from 2016-01-01)		
Microorganism	**Breakpoints (mg/L)**	
	Susceptible	**Resistant**
Staphylococcus spp. (S. aureus)	≤ 2[1]	> 2
Coagulase-negative staphylococcus	≤ 4[1]	> 4
Enterococcus spp.	≤ 4	> 4
Streptococcus ABCG	≤ 2[1]	> 2
Streptococcus pneumoniae	≤ 2[1]	> 2
Viridans group streptococci	≤ 2[1]	> 2
Gram-positive anaerobes	≤ 2	> 2
Clostridium difficile	≤ 2[2]	> 2[2]
Corynebacterium spp.	≤ 2	> 2

[1] Non-susceptible isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such isolate must be confirmed and the isolate sent to a reference laboratory.
[2] The breakpoints are based on epidemiological cut off values (ECOFFs), which distinguish wild type isolates from those with reduced susceptibility. 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.
Commonly susceptible species:

Gram-positive aerobes
Enterococcus faecalis
Staphylococcus aureus
Coagulase-negative *staphyloccoci*
Streptococcus group B
Streptococcus group C
Streptococcus group G
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans streptococci
Species for which acquired resistance may be a problem:
Gram-positive aerobes
Enterococcus faecium
Clostridium difficile (e.g. toxigenic strains implicated in pseudomembranous colitis) is a target species for oral use where high intraluminal concentrations of vancomycin are achieved.

5.2 Pharmacokinetic properties
Vancomycin is given intravenously for therapy of systemic infections.
In subjects with normal renal function, multiple intravenous dosing of 1 g of vancomycin (15 mg/kg) infused over 60 minutes produces mean plasma concentrations of approximately 63 mg/L immediately after the completion of infusion, mean plasma concentrations of approximately 23 mg/L 2 hours after infusion. Multiple dosing of 500 mg infused over 30 minutes produces mean plasma concentrations of about 49 mg/L at the completion of infusion, mean plasma concentrations of about 19 mg/L 2 hours after infusion, and mean plasma concentrations of about 10 mg/L 6 hours after infusion. The plasma concentrations during multiple dosing are similar to those after a single dose.
The mean elimination half-life of vancomycin from the plasma is 4 to 6 hours in patients with normal renal function. About 75% of an administered dose of vancomycin is excreted in urine by glomerular filtration in the first 24 hours.
Mean plasma clearance is about 0.058 L/kg/h, and mean renal clearance is about 0.048 L/kg/h. Renal vancomycin clearance is fairly constant and accounts for 70% to 80% of vancomycin elimination. The volume of distribution ranges from 0.39 to 0.97 L/kg. There is no apparent metabolism of the drug. Vancomycin is 55% protein bound as measured by ultrafiltration at vancomycin serum levels of 10 to 100 mg/L.
After IV administration of vancomycin hydrochloride, inhibitory concentrations are present in pleural, pericardial, ascitic, atrial appendage tissue and synovial fluid, as well as urine and peritoneal fluid. Vancomycin does not readily penetrate the cerebrospinal fluid unless the meninges are inflamed.
Renal dysfunction slows excretion of vancomycin. In anephric patients, the average half-life of elimination is 7.5 days.
The total systemic and renal clearance of vancomycin may be reduced in the elderly due to the natural decrement of glomerular filtration.
Vancomycin is not significantly absorbed from the normal gastro-intestinal tract and is therefore not effective by the oral route for infections other than staphylococcal enterocolitis and pseudomembranous colitis due to Clostridium difficile.
Orally administered vancomycin does not usually enter the systemic circulation even when inflammatory lesions are present. Measurable serum concentrations may occur infrequently in patients with active C. difficile-induced pseudomembranous colitis and, in the presence of renal impairment, the possibility of accumulation exists.
Administration of vancomycin oral solution, 2 g daily for 16 days to anephric patients with no inflammatory bowel disease, gave serum levels of <0.66 µg/ml. With doses of 2 g daily, concentration of 3,100 mg/kg can be found in the faeces and levels of <1 µg/ml can be found in the serum of patients with normal renal function who have pseudomembranous colitis.

5.3 Preclinical safety data
Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of vancomycin was found in standard laboratory tests. No definitive fertility studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None

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. Each parenteral solution should be checked visually for precipitation and discolouration prior to use.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Powder as packaged for sale:
2 years

Reconstituted concentrate:
The reconstituted concentrate should be further diluted immediately after reconstitution.

Diluted product:
From a microbiological and physicochemical point of view, the product should be used immediately.

6.4 Special precautions for storage

Powder as packaged for sale:
Store below 25°C.
Keep the vial in the outer carton in order to protect from light.

Reconstituted concentrate and diluted product:
For storage conditions of the reconstituted concentrate and diluted product, see section 6.3.

6.5 Nature and contents of container

Vancomycin - Fresenius 500 mg – Colourless type 1, 10 ml glass vial, with a chlorobutyl type1 silicone coated stopper and a grey aluminium/polypropylene flip-off cap.

Pack sizes: 1 vial, 10 x 1 vial, 50 x 1 vial

Vancomycin - Fresenius 1000 mg - Colourless type 1, 20 ml glass vial, with a chlorobutyl type1 silicone coated stopper and a green aluminium/polypropylene flip-off cap.

Pack sizes: 1 vial, 10 x 1 vial, 50 x 1 vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The product must be reconstituted and the resulting concentrate must then be diluted prior to use.

Preparation of the reconstituted concentrate:
Vancomycin - Fresenius 500 mg: Dissolve the content of each 500 mg vial in 10 ml of sterile water for injections.
Vancomycin - Fresenius 1000 mg: Dissolve the content of each 1000 mg vial in 20 ml of sterile water for injections.

Appearance of reconstituted concentrate:
Clear and colourless solution free from particles.

One ml of reconstituted concentrate contains 50 mg of vancomycin.

For storage conditions of the reconstituted concentrate, see sections 6.3

Preparation of final diluted solution infusion:
Reconstituted concentrate containing 50 mg/ml of vancomycin should be further diluted immediately after reconstitution.

Suitable diluents are:
Sodium Chloride 9 mg/ml (0.9%) Injection, Glucose 50 mg/ml (5%) Injection, Sodium Chloride 9 mg/ml (0.9 %) and Glucose 50 mg/ml (5%) Injection or Ringer acetate Injection.
Before administration, the reconstituted and diluted solutions should be inspected visually for particulate matter and discoloration. Only clear, and colourless solution free from particles should be used.

Intermittent infusion:
Vancomycin - Fresenius 500 mg : Reconstituted concentrate containing 500 mg of vancomycin (50 mg/ml) must be diluted further with at least 100 ml diluent immediately after reconstitution.
Vancomycin - Fresenius 1000 mg: Reconstituted concentrate containing 1000 mg of vancomycin (50 mg/ml) must be diluted further with at least 200 ml diluent immediately after reconstitution.

The concentration of vancomycin in Solution for infusion should not exceed 5 mg/ml.

The desired dose should be administered slowly by intravenous infusion at a rate of no more than 10 mg/minute, for at least 60 minutes or even longer.

For storage conditions of the diluted medicinal product, see sections 6.3

Disposal
Vials are for single use only. Unused product must be discarded.

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

7. Manufacturer
Fresenius Kabi Deutschland GmbH
D-61346 Bad Homburg, Germany.

8. Registration Holder:
Medic - Trim Healthcare Ltd
Post Maabarot 4023000, Israel

9. Product Registration No.:
Vancomycin - Fresenius 500 mg: 157-31-34457-00
Vancomycin - Fresenius 1000 mg: 157-32-34463-00

Prescription only medicine

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FRESENIUS KABI