PACKAGE LEAFLET: INFORMATION FOR THE USER

Vancomycin 500 mg
Vancomycin 1000 mg

powder for concentrate for solution for infusion

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. WHAT VANCOMYCIN IS AND WHAT IT IS USED FOR

Vancomycin is an antibiotic that belongs to a group of antibiotics called "glycopeptides". Vancomycin works by eliminating certain bacteria that cause infections.

Vancomycin powder is made into a solution for infusion.

Vancomycin is used in in all age groups by infusion for the treatment of the following serious infections:
- Infections of the skin and tissues below the skin.
- Infections of bone and joints.
- An infection of the lungs called "pneumonia".
- Infection of the inside lining of the heart (endocarditis) and to prevent endocarditis in patients at risk when undergoing major surgical procedures

2. WHAT YOU NEED TO KNOW BEFORE YOU USE VANCOMYCIN

Do not use Vancomycin

if you are allergic to vancomycin or any of the other ingredients of this medicine (listed in section 6).

Warning and precautions

Talk to your doctor or hospital pharmacist or nurse before using Vancomycin if:
- You suffered a previous allergic reaction to teicoplanin because this could mean you are also allergic to vancomycin.
- You have a hearing disorder, especially if you are elderly (you may need hearing tests during treatment).
- You have kidney disorder (you will need to have your blood and kidneys tested during treatment).
- You are receiving vancomycin by infusion for the treatment of the diarrhoea associated to *Clostridium difficile* infection instead of orally.

Talk to your doctor or hospital pharmacist or nurse during treatment with Vancomycin if:
- You are receiving vancomycin for a long time (you may need to have your blood, hepatic and kidneys tested during treatment).
- You develop any skin reaction during the treatment.
- You develop severe or prolonged diarrhoea during or after using vancomycin, consult your doctor immediately. This may be a sign of bowel inflammation (pseudomembranous colitis) which can occur following treatment with antibiotics.

Children

Vancomycin will be used with particular care in premature infants and young infants, because their kidneys are not fully developed and they may accumulate vancomycin in the blood. This age group may need blood tests for controlling vancomycin levels in blood.

Concomitant administration of vancomycin and anaesthetic agents has been associated with skin redness (erythema) and allergic reactions in children. Similarly, concomitant use with other medicines such as aminoglycoside antibiotics, nonsteroidal anti-inflammatory agents (NSAIDs, e.g., ibuprofen) or amphotericin B (medicine for fungal infection) can increase the risk of kidney damage and therefore more frequent blood and renal test may be necessary.

Other medicines and Vancomycin

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, herbal remedies or vitamins and minerals, because some of them could have an interaction with vancomycin. Furthermore, do not take any new medicine without consulting your doctor.

The following medicines can react with vancomycin if you take them at the same time, such as medicines for the treatment of:
- **infections caused by bacteria** (streptomycin, neomycin, gentamicin, kanamycin, amikacin, bacitracin, tobramycin, polymixin B, colistin),
- **tuberculosis** (viomycin),
- **fungal infections** (amphotericin B),
- **cancer** (cisplatin) *and*
- medicines for **muscle relaxation during anaesthesia**,
- **anaesthetic agents** (if you are going to have general anaesthesia).

Your doctor may need to monitor your blood and adjust the dosage if vancomycin is given at the same time with other medicines.

Pregnancy and breast-feeding

Pregnancy

If you are, or think you may be, pregnant, tell your doctor. Vancomycin should be given during pregnancy only if clearly needed.

Breast-feeding

Tell your doctor if you are breast-feeding as Vancomycin passes into breast milk. Your doctor will decide, if vancomycin is clearly needed or if you must stop breast-feeding.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Vancomycin has no or very little effect on your ability to drive and operate machines.

3. HOW TO USE VANCOMYCIN

You will be given Vancomycin by medical staff while you are in hospital.
Your doctor will decide how much of this medicine you should receive each day and how long the treatment will last.

Dosage

The dose given to you will depend on:
- your age,
- your weight,
- the infection you have,
- how well your kidneys are working,
- your hearing ability
- any other medicines you may be taking.

Intravenous administration

Adults and adolescents (from 12 years and older):

The dosage will be calculated according to your body weight. The usual infusion dose is 15 to 20 mg for each kg of body weight. It is usually given every 8 to 12 hours. In some cases, your doctor may decide to give an initial dose of up to 30 mg for each kg of body weight. The maximum daily dose should not exceed 2 g.

Use in children

Children aged from one month to less than 12 years of age:
The dosage will be calculated according to your body weight. The usual infusion dose is 10 to 15 mg for each kg of body weight. It is usually given every 6 hours.

Preterm and term newborn infants (from 0 to 27 days):
The dosage will be calculated according to 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).

The elderly, pregnant women and patients with a kidney disorder, including those on dialysis, may need a different dose.

Method of administration

Intravenous infusion means that the medicinal product flows from an infusion bottle or bag through a tube to one of your blood vessels and into your body. Your doctor, or nurse, will always give vancomycin into your blood and not in the muscle.

Vancomycin will be given into your vein for at least 60 minutes.

Duration of treatment

The length of treatment depends on the infection you have and may last a number of weeks.

The duration of the therapy may be different depending on the individual response to treatment for every patient.

During the treatment, you might have blood tests, be asked to provide urine samples and possibly have hearing tests to look for signs of possible side effects.

Vancomycin 500 mg powder for concentrate for solution for infusion
Vancomycin 1000 mg powder for concentrate for solution for infusion

The following information is intended for medical or healthcare professionals only:

This is an extract from the Summary of Product Characteristics to assist in the administration of Vancomycin. When determining appropriateness of use in a particular patient, the prescriber should be familiar with the Summary of Product Characteristics of the medicinal product.

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 interval of administration

Patients aged 12 years and older

The recommended dose is 15 to 20 mg/kg of body weight every 8 to 12 h (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 target trough 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 (see section 4.4 of the SmPC).

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: (see section 4.4 of the SmPC).

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

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

Peri-operative prophylaxis of bacterial endocarditis in all age groups

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

Duration of treatment

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

Indication	Treatment duration
Complicated skin and soft tissue infections • Non necrotizing • Necrotizing	 7 to 14 days 4 to 6 weeks*
Bone and joint infections	4 to 6 weeks**
Community-acquired pneumonia	7 to 14 days
Hospital-acquired pneumonia, including ventilator-associated pneumonia	7 to 14 days
Infective endocarditis	4 to 6 weeks***

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

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

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

Special populations

Elderly

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

Renal impairment

In adult and paediatric 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 (see section 4.4 of the SmPC).

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

Adults

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

Men: [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 (see section 4.4 of the SmPC). 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.

Paediatric population

Dose adjustments in paediatric patients aged 1 year and older could be based on glomerular filtration rate estimated (eGFR) by the revised Schwartz formula:
eGFR (mL/min/1.73m2) = (height cm x 0.413)/ serum creatinine (mg/dl)
eGFR (mL/min/1.73m2) = (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 is not applicable to them.

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

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

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

Hepatic impairment

No dose adjustment is needed in patients with hepatic insufficiency.

Pregnancy

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Vancomycin can cause allergic reactions, although serious allergic reactions (anaphylactic shock) are rare. Tell your doctor immediately if you get any sudden wheeziness, difficulty in breathing, redness on the upper part of the body, rash or itching.

Common side effects (may affect up to 1 in 10 people):
- Fall in blood pressure
- Breathlessness, noisy breathing (a high-pitched sound resulting from obstructed air flow in the upper airway)
- Rash and inflammation of the lining of the mouth, itching, itching rash, hives
- Kidney problems which may be detected primarily by blood tests
- Redness of upper body and face, inflammation of a vein

Uncommon side effects (may affect up to 1 in 100 people):
- Temporary or permanent loss of hearing.

Rare side effects (may affect up to 1 in 1,000 people):
- Decrease in white blood cells, red blood cells and platelets (blood cells responsible for blood clotting)
- Increase in some of the white cells in the blood.
- Loss of balance, ringing in your ears, dizziness
- Blood vessel inflammation
- Nausea (feeling sick)
- Inflammation of the kidneys and kidney failure
- Pain in the chest and back muscles
- Fever, chills

Very rare side effects (may affect up to 1 in 10,000 people):
- Sudden onset of severe allergic skin reaction with skin flaking blistering or peeling skin. This may be associated with a high fever and joint pains
- Cardiac arrest
- Inflammation of the bowel which causes abdominal pain and diarrhea, which may contain blood

Not known (frequency cannot be estimated from the available data):
- Being sick (throwing up), diarrhoea
- Confusion, drowsiness, lack of energy, swelling, fluid retention, decreased urine
- Rash with swelling or pain behind the ears, in the neck, groin, under the chin and armpits (swollen lymph nodes), abnormal blood and liver function tests
- Rash with blisters and fever.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE VANCOMYCIN

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton, after EXP: (month/year). The expiry date refers to the last day of that month.

Do not store above 25 ºC.

Reconstituted concentrate:
After reconstitution, the reconstituted concentrate should be diluted immediately.

Further diluted solution:
Chemical and physical in-use stability has been demonstrated for 48 hours at 2º-8ºC and 25ºC with Sodium Chloride 9 mg/ml (0.9%) Injection and Glucose 50 mg/ml (5%) Injection.
From a microbiological point of view, unless the method of reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.
Keep the vial in the outer carton in order to protect from light.

Do not use this medicine if you notice an unclear solution and extraneous particles.
The stability of reconstituted solution is stated below in the additional information for health professionals.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Vancomycin contains
- The active substance is vancomycin (as hydrochloride).
- There are no other ingredients.

Vancomycin 500 mg powder for concentrate for solution for infusion
Each vial contains 500 mg vancomycin (as hydrochloride) equivalent to 500,000 IU vancomycin.
When reconstituted with 10 ml of water for injections, the resulting concentrate for solution for infusion contains 50 mg/ml vancomycin.

Vancomycin 1000 mg powder for concentrate for solution for infusion
Each vial contains 1000 mg vancomycin (as hydrochloride) equivalent to 1,000,000 IU vancomycin.
When reconstituted with 20 ml of water for injections, the resulting concentrate for solution for infusion contains 50 mg/ml vancomycin.

What Vancomycin looks like and contents of the pack

This medicine is a homogeneous, white to off-white freeze-dried powder for concentrate for solution for infusion. It must be first dissolved in water for injection and further diluted in an appropriate diluent prior to use.

This medicine is supplied in transparent glass vials closed with rubber stopper and sealed with aluminium and plastic flip-off caps. This medicine is available in two strengths: 500 mg and 1000 mg

Vancomycin is packed in carton boxes. Each box can contain 1 or 10 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturers

Marketing Authorisation Holder:
Hikma Farmacêutica (Portugal), S.A.
Estrada do Rio da Mó n.º 8, 8A e 8B – Fervença 2705-906 Terrugem SNT, Portugal

Manufacturers:
Hikma Italia S.pA.
Viale Certosa, 10, 27100 Pavia, Italy

Hikma Farmacêutica (Portugal), S.A.
Estrada do Rio da Mó n.º 8, 8A e 8B – Fervença 2705-906 Terrugem SNT, Portugal

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Other sources of information
Advice/medical education
Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.

If your doctor has prescribed antibiotics, you need them precisely for your current illness.

Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.

Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:
- dosage
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:
1. Use antibiotics only when prescribed.
2. Strictly follow the prescription.
3. Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.

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Obese patients
In obese patients, the initial dose should be individually adapted according to total body weight as in non-obese patients. Modification of the usual daily doses may be required.

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

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

Therapeutic trough (minimum) vancomycin blood levels should normally be 10-20 mg/l, depending on the site of infection and susceptibility of the pathogen. Trough values of 15-20 mg/l are usually recommended by clinical laboratories to better cover susceptible-classified pathogens with MIC ≥1 mg/L (see sections 4.4 and 5.1 of the SmPC).

Model-based methods may be useful in the prediction of individual dose requirements to reach an adequate AUC. The model-based approach can be used both in calculating the personalized starting dose and for dose adjustments based on TDM results (see section 5.1 of the SmPC).

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 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) (see section 4.4 of the SmPC).

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.
For information about the preparation of the solution, please see section 6.6 of the SmPC.
Continuous vancomycin infusion may be considered, e.g., in patients with unstable vancomycin clearance.

Interaction with other medicinal products and other forms of interaction

Other potentially nephrotoxic or ototoxic medications
Concurrent or sequential administration of vancomycin with other potentially neurotoxic or/and nephrotoxic active substances particularly gentamycin, amphotericin B, streptomycin, neomycin, kanamycin, amikacin, tobramycin, viomycin, bacitracin, polymyxin B, colistin and cisplatin may potentiate the nephrotoxicity and/or ototoxicity of vancomycin and consequently requires careful monitoring of the patient.

Because of synergic action (e.g. with gentamycin) in these cases the maximum dose of vancomycin has to be restricted to 500 mg every 8 hours.

Anaesthetics
Concurrent administration of vancomycin and anaesthetic agents has been associated with erythema, histamine like flushing and anaphylactoid reactions. This may be reduced if the vancomycin is administered over 60 minutes before anaesthetic induction.

Muscle relaxants
If vancomycin is administered during or directly after surgery, the effect (neuromuscular blockade) of muscle relaxants (such as succinylcholine) concurrently used can be enhanced and prolonged.

Incompatibilities

Vancomycin has a low pH that may cause chemical or physical instability when it is mixed with other substances. Therefore, each parenteral solution should be checked visually for precipitations and discolouration prior to use.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6 of the SmPC.

Combination therapy
In case of combination therapy of vancomycin with other antibiotics/ chemotherapeutics, the preparations should be administered separately.

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

Shelf life

Powder: 2 years

Reconstituted concentrate:
Chemical and physical in-use stability has been demonstrated for 48 hours at 2º-8ºC and 25ºC.
After reconstitution, the reconstituted concentrate should be diluted immediately.

Further diluted solution:
Chemical and physical in-use stability has been demonstrated for 48 hours at 2º-8ºC and 25ºC with Sodium Chloride 9 mg/ml (0.9%) Injection and Glucose 50 mg/ml (5%) Injection.

From a microbiological point of view, unless the method of reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

Special precautions for disposal and other handling

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

Preparation of the reconstituted concentrate
Dissolve Vancomycin 500 mg Powder for concentrate for solution for infusion in 10 ml of sterile Water for injection.
Dissolve Vancomycin 1000 mg Powder for concentrate for solution for infusion in 20 ml of sterile Water for injection.

One ml of **reconstituted concentrate** contains 50 mg of vancomycin.

Appearance of reconstituted concentrate
After reconstitution the solution is clear and colourless to slightly yellowish brown without visible particles.

For storage conditions of the reconstituted medicinal product, see section 6.3 of the SmPC.

Preparation of final diluted Solution for infusion
Reconstituted solutions containing 50 mg/ml of vancomycin should be further diluted.

Suitable diluents are:
Sodium Chloride 9 mg/ml (0.9%) Injection
Glucose 50 mg/ml (5%) Injection

Intermittent infusion:
Reconstituted solution containing 500 mg vancomycin (50 mg/ml) must be diluted further with at least 100 ml diluent (to 5 mg/ml).
Reconstituted solution containing 1000 mg vancomycin (50 mg/ml) must be diluted further with at least 200 ml diluent (to 5 mg/ml).

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

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

Continuous infusion:
This should be used only if treatment with an intermittent infusion is not possible. Dilute 1000 mg to 2000 mg of dissolved vancomycin in a sufficient amount of the above suitable diluent and administer it in the form of a drip infusion, so that the patient will receive the prescribed daily dose in 24 hours.

Appearance of diluted solution
After dilution, the solution is clear, free from extraneous particles.

For storage conditions of the diluted medicinal product, see section 6.3 of the SmPC.

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.

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.