PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

VANCOCIN® CP 500 mg (Powder for injection)

VANCOCIN® CP 1 g (Powder for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Vancocin CP 500 mg (chromatographically purified) vial contains sterile vancomycin hydrochloride equivalent to 500 mg of vancomycin base / 10 ml of reconstituted solution.

Each Vancocin CP 1 g (chromatographically purified) vial contains sterile vancomycin hydrochloride equivalent to 1 g of vancomycin base / 20 ml of reconstituted solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vancocin CP 500 mg (powder for injection), is a 10 ml size vial sealed with a rubber stopper and an aluminium cap. It contains a white to off-white coloured, dry, sterile powder for injection. When reconstituted in water it is a clear and colourless to light-yellow solution.

Vancocin CP 1 g (powder for injection), is a 20 ml size vial sealed with a rubber stopper and an aluminium cap. It contains a white to off-white coloured, dry, sterile powder for injection. When reconstituted in water it is a clear and colourless to light-yellow solution.

Vancocin CP is a tricyclic glycopeptide antibiotic derived from *Streptomyces orientalis*. When reconstituted in water it has a pH range of 2,5 to 4,5. The chemical formula is $C_{66}H_{75}Cl_2N_9O_{24}$, with a molecular mass of 1 449; 500 mg of the base is equivalent to 0,35 mmol.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

VANCOCIN CP is indicated in therapy of methicillin-resistant (β-lactam-resistant) staphylococcal infections. It is also indicated in therapy of serious staphylococcal infections in penicillin-allergic patients or in patients who have failed to respond to the penicillins or cephalosporins.

VANCOCIN CP is indicated in patients with serious infections caused by other vancomycin-sensitive organisms that are resistant to other antimicrobial medicines, including the penicillins or cephalosporins. VANCOCIN CP is indicated for initial therapy when methicillin-resistant staphylococci are suspected, but once sensitivity data are available, therapy should be adjusted accordingly.
VANCOCIN CP is indicated in the treatment of staphylococcal endocarditis. It may be indicated in serious infections due to staphylococci. When staphylococcal infections are localised and purulent, antibiotics are used as adjuncts to appropriate surgical measures.

In penicillin-allergic patients, VANCOCIN CP is indicated alone or in combination with an aminoglycoside for endocarditis caused by *S. viridans* or *S. bovis*. For endocarditis caused by enterococci (e.g. *E. faecalis*), VANCOCIN CP should be used in combination with an aminoglycoside.
Specimens for bacteriologic cultures should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to VANCOCIN CP.

The parenteral form of VANCOCIN CP may be administered orally for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis produced by *C. difficile*.

Parenteral administration of VANCOCIN CP alone is of unproven benefit for these indications. VANCOCIN CP is not effective by the oral route for other types of infection.

4.2. Posology and method of administration

Posology:

Patients with normal renal function:

Adults:

The usual daily intravenous dose is 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours. Each dose should be administered at a rate of no more than 500 mg per half-hour.

Children:

The total daily intravenous dosage of VANCOCIN CP, calculated on the basis of 40 mg/kg of body mass, can be divided and incorporated into the child's 24-hour fluid requirement. Each dose should be administered at a rate of no more than 500 mg per half-hour.

Infants and neonates:

In neonates and young infants, the total daily intravenous dosage is lower. An initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours in the first week of life and every 8 hours thereafter until one month of age. Close monitoring of serum VANCOCIN CP concentrations is warranted in these patients.

Patients with impaired renal function:

Dosage adjustment must be made in patients with impaired renal function. Measurement of vancomycin serum concentrations can be helpful in order to optimise therapy, especially in seriously ill patients with changing renal function.

For most patients with renal impairment, or the elderly, the dosage calculation may be made by using the following table if the creatinine clearance can be measured or estimated accurately. The

VANCOCIN CP dose per day in mg is about 15 times the glomerular filtration rate in ml/min (see table below).

Dosage table for vancomycin in patients with impaired renal function:

Creatinine Clearance (ml /min)	***Vancomycin Dose (mg/24 hours)***
100	1 545
90	1 390
80	1 235
70	1 080
60	925
50	770
40	620
30	465
20	310
10	155

The initial dose should be no less than 15 mg/kg even in patients with mild to moderate renal insufficiency.

The table is not valid for functionally anephric patients. For such patients, an initial dose of 15 mg/kg of body mass should be given in order to promptly achieve therapeutic serum concentrations. The dose required to maintain stable concentrations is 15 mg/kg weekly. As individual maintenance doses of 250 to 1 000 mg are convenient in patients with marked renal impairment, a dose may be given every several days rather than on a daily basis.

Intermittent intravenous infusion:

Intermittent infusion is the preferred method of administration. At the time of use, add 10 ml of sterile water for injection to the 500 mg vial or 20 ml of sterile water for injection to the 1 g vial of

dry, sterile vancomycin powder. The reconstituted solution containing 500 mg of vancomycin must be diluted with at least 100 ml of diluent. Reconstituted solutions containing 1 g must be diluted with at least 200 ml of diluent. The desired dose, diluted in this manner, may be administered by intravenous infusion at a rate of no more than 500 mg per half-hour.

Compatibility with intravenous fluids:

Solutions that are diluted with 5 % dextrose injection or 0,9 % sodium chloride injection may be stored in a refrigerator for 14 days without significant loss of potency.

Solutions that are diluted with the following infusion fluids may be stored in a refrigerator for 96 hours: 5 % Dextrose and 0,9 % Sodium Chloride injection, USP, Lactated Ringer's injection, USP, Lactated Ringer's and 5 % Dextrose injection, Normosol-M and 5 % Dextrose, Acetated Ringer's injection.

Vancomycin solution has a low pH and may cause physical instability of other compounds. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution or container permits.

For oral administration:

The usual adult total daily dosage for antibiotic-associated pseudomembranous colitis produced by *C. difficile* is 500 mg to 2 g given in 3 or 4 divided doses for 7 to 10 days. The total daily dosage in children is 40 mg/kg of body mass in 3 or 4 divided doses. The total daily dosage should not exceed 2 g. The appropriate dose should be diluted in 30 ml of water and given to the patient to drink. Common flavouring syrups should be added to the solution to disguise the taste for oral administration.

4.3. Contraindications

VANCOCIN CP is contra-indicated in patients with known hypersensitivity to this antibiotic.

4.4. Special warnings and precautions for use

VANCOCIN CP should be administered in a dilute solution at a rate of no more than 500 mg per half-hour to avoid rapid-infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions (see section 4.2).

Dosage of VANCOCIN CP must be adjusted for patients with renal dysfunction (see section 4.2). When treating patients with underlying renal dysfunction or those patients receiving concomitant therapy with an aminoglycoside, serial monitoring of renal function should be performed, and particular care should be taken in following appropriate dosing schedules in order to minimise the risk of nephrotoxicity.

Pseudomembranous colitis has been reported with many broad-spectrum antibiotics, including intravenous vancomycin, therefore it is important to consider its diagnosis in patients who develop diarrhoea in association with their use.

Such colitis may be life-threatening and appropriate measures should be taken, including discontinuation of the antibiotic.

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 generalised 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.

General:

Ototoxicity has occurred in patients receiving VANCOCIN CP. It may be transient or permanent. It has been reported mostly in patients who have been given excessive doses, have an underlying hearing loss and deafness, or are receiving concomitant therapy with another ototoxic medicine such as an aminoglycoside. Monitoring of auditory function is advised especially in the elderly. Reversible neutropenia has been reported in patients receiving VANCOCIN CP. Periodic monitoring of the leucocyte count is prudent.

VANCOCIN CP is irritating to tissue and must be given by a secure intravenous route of administration. Pain, tenderness and necrosis occur with intramuscular injection of VANCOCIN CP or with inadvertent extravasation. Thrombophlebitis may occur, the frequency and severity of which can be minimised by administering the medicine slowly as a dilute solution and by rotating the sites of infusion.

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 section 4.2 and 4.5).

Eye disorders:

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

Haemorrhagic 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.

Paediatrics (see "General"):

In premature neonates and young infants, it may be appropriate to confirm desired vancomycin serum concentrations.

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.

Geriatrics (see "General"):

The natural decrease in 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.

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

Other ototoxic or nephrotoxic medicines, such as the aminoglycosides, polymyxins, and loop diuretics, markedly increase the risk of toxicity and should be given concomitantly with vancomycin only with great caution.

Some of the adverse effects of vancomycin may be enhanced by the concurrent use of general anaesthetics; it has been suggested that, where patients require both, vancomycin infusion should be completed before the induction of anaesthesia.

Concomitant administration of vancomycin and anaesthetic medicines has been associated with erythema and histamine-like flushing in children.

Vancomycin may increase neuromuscular blockade produced by medicines such as suxamethonium or vecuronium.

There have been reports that the frequency of infusion-related events increases with the concomitant administration of anaesthetic agents. Infusion-related events may be minimised by the administration of vancomycin as a 60-minute infusion prior to anaesthetic induction. When administered during anaesthesia, doses must be diluted to 5 mg/ml or less and administered slowly with close cardiac monitoring. Position changes should be delayed until the infusion is completed to allow for postural adjustment.

Concurrent or sequential systemic or topical use of other potentially ototoxic or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymixin B, colistin, viomycin, cisplatin, loop diuretics, piperacillin/tazobactam and NSAIDs may increase the toxicity of vancomycin and if they need to be given should be used with caution and appropriate monitoring.

4.6 Fertility, pregnancy and lactation

Pregnancy:

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.

Breastfeeding:

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

4.7. Effects on ability to drive and use machines

It is advisable to exercise caution when driving or operating machinery.

4.8. Undesirable effects

The following side effects have been reported:

Renal and urinary disorders:

Less frequent: Nephrotoxicity.

There have been reports of increased serum creatinine and urea concentrations in patients given VANCOCIN CP.

This is an indication to stop VANCOCIN CP administration. Interstitial nephritis and renal failure have been reported.

Ear and labyrinth disorders:

Less frequent: Ototoxicity. Hearing loss and deafness have been reported.

Most patients had kidney dysfunction, pre-existing hearing loss, or concomitant treatment with another ototoxic medicine. Vertigo, dizziness, and tinnitus have been reported.

Blood and lymphatic system disorders:

Less frequent: Reversible neutropenia, usually starting one week or more after onset of therapy with VANCOCIN CP or after a total dose of more than 25 g, may occur. Neutropenia appears to be promptly reversible when VANCOCIN CP is discontinued. Thrombocytopenia, agranulocytosis and eosinophilia have been reported.

Gastrointestinal disorders:

Less frequent: Nausea and vomiting. Bitter or unpleasant taste with the oral solution.

Less frequent: Chemical peritonitis and pseudomembranous colitis have been reported.

Skin and subcutaneous tissue disorders:

Frequent: Flushing of the upper body (“red man syndrome”), exanthema and mucosal inflammation, pruritus, urticaria.

Less frequent: Rashes (including exfoliative dermatitis), Stevens-Johnson syndrome, toxic epidermal necrolysis, linear IgA bullous dermatosis and rare cases of vasculitis in association with VANCOCIN CP have been reported.

Frequency unknown:

Eosinophilia and systemic symptoms (DRESS syndrome), AGEP (Acute Generalised Exanthematous Pustulosis).

Cardiac disorders:

Less frequent: Cardiac arrest has been reported.

General disorders and administration site conditions:

Pain, inflammation, necrosis and thrombophlebitis at the injection site have been reported.

Frequent: Phlebitis, redness of the upper body and face.

Less frequent: Drug fever, shivering, Pain and muscle spasm of the chest and back muscles.

Other:

Infusion-related events:

During or soon after rapid infusion of VANCOCIN CP, patients may develop anaphylactoid reactions including hypotension, wheezing, dyspnoea, urticaria or pruritus. Rapid infusion may also cause flushing of the upper body ("red neck") or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes of stopping the infusion.

Patients have been reported to have had hypersensitivity reactions, anaphylaxis and medicine fever after using VANCOCIN CP.

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the

"**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Suspected adverse reactions can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9. Overdose

Supportive care is advised, with maintenance of glomerular filtration. Although vancomycin is not effectively removed by either haemodialysis or peritoneal dialysis, there have been reports of increased vancomycin clearance with haemoperfusion and haemofiltration.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: glycopeptide antibacterials

ATC Code: J01 XA01 for intravenous use and A07 AA09 for oral use.

Mechanism of action:

Vancomycin is a tricyclic glycopeptide antibiotic that inhibits the synthesis of the cell wall in sensitive bacteria by binding with high affinity to the D-alanyl-D-alanine terminus of cell wall precursor units. The drug is slowly bactericidal for dividing microorganisms. In addition, it impairs the permeability of the bacterial cell membrane and RNA synthesis.

Mechanism of resistance:

Microbiology:

The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial cell membrane permeability and RNA synthesis.

Vancomycin is active against:

Staphylococcus aureus (including heterogeneous methicillin-resistant strains).

Staphylococcus epidermidis (including heterogeneous methicillin-resistant strains).

Streptococcus pyogenes.

Streptococcus pneumoniae.

Streptococcus agalactiae.

Viridans group of streptococci.

Streptococcus bovis.

Enterococci (eg *Enterococcus faecalis* [formerly *Streptococcus faecalis*]) - provided vancomycin is used in combination with aminoglycosides.

Clostridium difficile (eg toxigenic strains implicated in pseudomembranous enterocolitis).

Diphtheroids.

Vancomycin is active, in vitro, against:

Listeria monocytogenes.

Lactobacillus sp.

Actinomyces sp.

Clostridium sp.

Bacillus sp.

Vancomycin is not active *in vitro* against gram-negative bacilli, mycobacteria or fungi.

Synergy:

The combination of vancomycin and an aminoglycoside acts synergistically against many strains of *S. aureus*, non-enterococcal group D streptococci, enterococci and *Streptococcus* species (viridans group). The combination of vancomycin and a cephalosporin acts synergistically against some strains of *S. epidermidis* (methicillin-resistant). The combination of vancomycin and rifampicin acts with partial synergism against some strains of *S. aureus* and with synergism against *S. epidermidis*. Synergy testing is helpful because the combination of vancomycin and a cephalosporin may act antagonistically against some strains of *S. epidermidis* and the combination of vancomycin and rifampicin may act with antagonism against some strains of *S. aureus*.

In vitro sensitivity does not imply *in vivo* activity.

5.2. Pharmacokinetic properties

Clinical pharmacology:

Vancomycin is poorly absorbed after oral administration; it is given intravenously for therapy of systemic infections. Intramuscular injection is painful.

The mean elimination half-life of vancomycin from plasma is 4 to 6 hours in patients with normal renal function. In the first 24 hours, about 75 % of an administered dose of vancomycin is excreted in urine by glomerular filtration. Renal dysfunction slows excretion of vancomycin. In anephric patients, the average half-life of elimination is 7,5 days. There is no apparent metabolism of the medicine. About 60 % of an intraperitoneal dose of vancomycin administered during peritoneal dialysis is absorbed systemically in 6 hours. Significant serum concentrations may be reached with intraperitoneal administration.

Binding of vancomycin to human serum protein is approximately 55 % as measured by ultrafiltration at vancomycin serum concentrations of 10 to 100 mg/l. After IV administration of vancomycin, inhibitory concentrations are present in pleural, pericardial, ascitic and synovial fluids, in urine, in peritoneal dialysis fluid, and in atrial appendage tissue. Vancomycin does not readily diffuse across normal meninges into the spinal fluid, but when the meninges are inflamed, penetration into the spinal fluid occurs.

After multiple oral administration of vancomycin, measurable serum concentrations may occur in patients with active *Clostridium difficile*-induced pseudomembranous colitis.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Water for injection

6.2. Incompatibilities

Not applicable

6.3. Shelf life

2 years

6.4. Special precautions for storage

Before reconstitution:

Store at or below 25 °C.

After reconstitution:

The solution has a satisfactory potency for 24 hours when stored at 15 to 25 °C. When reconstituted with water for injection; 5 % dextrose injection; or 0,9 % sodium chloride injection, the product is stable for 14 days when stored in a refrigerator (0 to 5 °C).
When reconstituted with 5 % dextrose and 0,9 % sodium chloride injection, USP; lactated Ringer's injection, USP; lactated Ringer's and 5 % dextrose injection; Normosol-M and 5 % dextrose; Isolyte E; or acetated Ringer's injection, the product is stable for 96 hours when stored in a refrigerator (0 to 5 °C).

6.5. Nature and contents of container

Vancocin CP 500 mg (powder for injection) 10 ml vials are supplied in packs of 1 or 10.
Vancocin CP 1 g (powder for injection) 20 ml vials are supplied in packs of 1 or 10.

6.6. Special precautions for disposal and other handling

Preparation of solution*:* At the time of use, add 10 ml of Water for injections Ph.Eur to the 500 mg vial, or 20 ml Water for injections Ph.Eur to the 1000 mg vial. Vials reconstituted in this manner will give a solution of 50 mg/ml.
FURTHER DILUTION IS REQUIRED. Read instructions which follow:

Intermittent infusion: is the preferred method of administration. Reconstituted solutions containing 500 mg vancomycin must be diluted with at least 100 ml diluent. Reconstituted solutions containing 1000 mg vancomycin must be diluted with at least 200 ml diluent. Sodium Chloride Intravenous Infusion BP or 5 % Dextrose Intravenous Infusion BP are suitable diluents. The desired dose should be given by intravenous infusion over a period of at least 60 minutes. If administered over a shorter period of time or in higher concentrations, there is the possibility of inducing marked hypotension in addition to thrombophlebitis. Rapid administration may also produce flushing and a transient rash over the neck and shoulders.

Continuous infusion: (should be used only when intermittent infusion is not feasible). 1000-2000 mg can be added to a sufficiently large volume of Sodium Chloride Intravenous Infusion BP or 5 % Dextrose Intravenous Infusion BP to permit the desired daily dose to be administered slowly by intravenous drip over a 24-hour period.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-Ir

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBERS

Vancocin CP 500 mg: C/20.1.1/181

Vancocin CP 1 g: X/20.1.1/23

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Vancocin CP 500 mg: 22 February 1971

Vancocin CP 1 g: 13 July 1989

10. DATE OF REVISION OF THE TEXT

09 April 2021

[1]Company Reg. No.: 1990/001979/07

Additional countries registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	Vancocin CP 500 mg	S2	B9303365
	Vancocin CP 1 g	S2	BOT9700062
Namibia	Vancocin CP 500 mg	NS2	90/20.1.1/00558
	Vancocin CP 1 g	NS2	90/20.1.1/00557
Zambia	Vancocin CP 500 mg	POM	039/047
	Vancocin CP 1 g	POM	039/046

ATC Code: J01XA01- Glycopeptide antibacterials

Name and address of manufacturer:

Lek Pharmaceutical d.d.
Verovškova 57
SI-1526 Ljubljana
Slovenia