SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vancomycin hydrochloride for Injection USP 1 gm

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Vancomycin hydrochloride USP
eq.to Vancomycin 1 gm

3. PHARMACEUTICAL FORM

Powder for Injection
A white crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravenous administration
Vancomycin is indicated in all age groups for the treatment of the following infections:
• complicated skin and soft tissue infections (cSSTI)
• bone and joint infections
• community acquired pneumonia (CAP)
• hospital acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP)
• infective endocarditis
• bacteraemia that occurs in association with, or is suspected to be associated with any of the above.
Vancomycin is also indicated in all age groups for the perioperative antibacterial prophylaxis in patients that are at high risk of developing bacterial endocarditis when undergoing major surgical procedures.

4.2 Posology and method of administration

Posology
Where appropriate, vancomycin should be administered in combination with other antibacterial agents.
Intravenous administration
The initial dose should be based on total body weight. Subsequent dose adjustments should be based on serum concentrations to achieve targeted therapeutic concentrations. Renal function must be taken into consideration for subsequent doses and 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 2g 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.
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:

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	
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 with suitable antibiotics 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.

Vancomycin is poorly dialyzable by intermittent haemodialysis. 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. 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/1.73m^2) = (height cm x 0.413)/ serum creatinine (mg/dl)
eGFR (mL/min/1.73m^2)= (height cm x 36.2/serum creatinine (µmol/L)
For neonates and infants below 1 year of age, expert advice should be sought as the revised Schwartz formula 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**	**Frequency**
50-30	15 mg/kg	12 hourly
29-10	15 mg/kg	24 hourly
< 10	10-15 mg/kg	Re-dose based on levels*
Intermittent haemodialysis		
Peritoneal dialysis		
Continuous renal replacement therapy	15 mg/kg	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.
Obese patients
In obese patients, the initial dose should be individually adapted according to total body weight as in non-obese patients.
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).
Patients whose fluid intake must be limited can also receive a solution of 500 mg/50 ml or 1000 mg/100 ml, although the risk of infusion-related undesirable effects can be increased with these higher concentrations.
Continuous vancomycin infusion may be considered, e.g., in patients with unstable vancomycin clearance.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
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. 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 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. This may be reduced by administering vancomycin by infusion over at least 60 minutes, before anaesthetic induction.

Severe bullous reactions

Stevens-Johnson syndrome (SJS) has been reported with the use of vancomycin. If symptoms or signs of SJS (e.g. progressive skin rash often with blisters or mucosal lesions) are present, vancomycin treatment should be discontinued immediately and specialised dermatological assessment be sought.

Administration site related reactions

Pain and thrombophlebitis may occur in many patients receiving intravenous vancomycin and are occasionally severe. The frequency and severity of thrombophlebitis can be minimized by administering the medicinal product slowly as a dilute solution and by changing the sites of infusion regularly.

The efficacy and safety of vancomycin has not been established for the intrathecal, intralumbar and intraventricular routes of administration.

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.

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

4.6 Fertility, pregnancy and lactation
Pregnancy
No sufficient safety experience is available regarding vancomycin during human pregnancy. Reproduction toxicological studies on animals do not suggest any effects on the development of the embryo, foetus or gestation priod.
However, vancomycin penetrates the placenta and a potential risk of embryonal and neonatal ototoxicity and nephrotoxicity cannot be excluded. Therefore vancomycin should be given in pregnancy only if clearly needed and after a careful risk/benefit evaluation.
Lactation:
Vancomycin is excreted in human milk and should be therefore used in lactation period only if clearly necessary. Vancomycin should be cautiously given to breast-feeding mothers because of potential adverse reactions in the infant (disturbances in the intestinal flora with diarrhoea, colonisation with yeast-like fungi and possibly sensibilisation).
Considering the importance of this medicine for nursing mother, the decision to stop breastfeeding should be considered.

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.
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.
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
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, Linear IgA bullous dermatosis[5], Toxic epidermal necrolysis (TEN)
Not known	Eosinophilia and systemic symptoms (DRESS syndrome), AGEP (Acute Generalized Exanthematous Pustulosis)
Renal and urinary disorders:	
Common	Renal insufficiency manifested primarily by increased serum creatinine and serum urea
Rare	Interstitial nephritis, acute renal failure.
Not known	Acute tubular necrosis
General disorders and administration site conditions:	
Common	Phlebitis, redness of the upper body and face.
Rare	Drug fever, shivering, pain and muscle spasm of the chest and back muscles

Description of selected adverse drug reactions

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

During or shortly after rapid infusion anaphylactic/ anaphylactoid reactions including wheezing may occur. The reactions abate when administration is stopped, generally between 20 minutes and 2 hours. Vancomycin should be infused slowly. Necrosis may occur after intramuscular injection.

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

Ototoxicity has primarily been reported in patients given high doses, or in those on concomitant treatment with other ototoxic medicinal products like aminoglycosides, or in those who had a pre-existing reduction in kidney function or hearing.
If a bullous disorder is suspected, the drug should be discontinued and specialised dermatological assessment should be carried out.
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.

4.9 Overdose
Toxicity due to overdose has been reported. 500 mg iv to a child, 2 year of age, resulted in lethal intoxication. Administration of a total of 56 g during 10 days to an adult resulted in renal insufficiency. In certain high-risk conditions (e. g. in case of severe renal impairment) high serum levels and oto- and nephrotoxic effects can occur.
Measures in case of overdose:
• A specific antidote is not known.
• Symptomatic treatment while maintaining renal function is required
• 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
Pharmacotherapeutic group: Anti-infectives. Antibacterials. Other antibacterials.
ATC Code: J01XA01 – Anti-infectives for systemic use – Antibacterials for systemic use – Other antibacterials – Glycopeptide antibacterials.
Mechanism of action
Vancomycin is a tricyclic glycopeptide antibiotic that inhibits the synthesis of the cell wall in sensitive bacteria by binding with high affinity to the D-alanyl-D-alanine terminus of cell wall precursor units. The drug is slowly bactericidal for dividing microorganisms. In addition, it impairs the permeability of the bacterial cell membrane and RNA synthesis.
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.
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.

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 1g 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.
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.

5.3 Preclinical safety data

Not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
No excipients

6.2 Incompatibilities
Not known.

6.3 Shelf life
36 Months

6.4 Special precautions for storage
Store below 30°C. Protect from light.
Keep out of reach of children.

6.5 Nature and contents of container and special equipment for use, administration or implantation
20 ml USP type III flint clear, colourless moulded glass vial plugged with 20mm grey butyl rubber and sealed with 20mm flip off aluminium seal.

6.6 Special precautions for disposal and other handling
None.

7. MARKETING AUTHORISATION HOLDER
Ciron Drugs & Pharmaceuticals Pvt. Ltd.
C- 1101 /1102, Lotus Corporate Park, Graham Firth Steel Compound,
Jay Coach Junction, Western Express Highway, Goregaon (East)
Mumbai- 400 063, India.

8. MARKETING AUTHORISATION NUMBER(S)
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10. DATE OF REVISION OF THE TEXT
14/07/2023

11. Reference
https://www.medicines.org.uk/emc/product/8760/smpc#gref