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# Cinva™ IV Injection

(Vancomycin)

Lyophilized injection for infusion

سین وا انجکشن

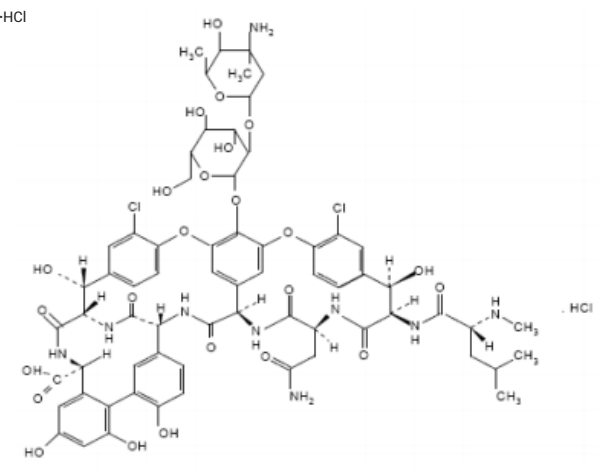
**COMPOSITION:**
***Cinva Injection 500 mg:***
Each vial of lyophilized powder contains:
Vancomycin hydrochloride USP
equivalent to Vancomycin ..... 500 mg.

**Product Specs.:** USP

***Cinva Injection 1 gm:***
Each vial of lyophilized powder contains:
Vancomycin hydrochloride USP
equivalent to Vancomycin ..... 1 gm.

**Product Specs.:** USP

**DESCRIPTION:**
Vancomycin hydrochloride is a white to off-white, hygroscopic powder. It forms a clear, colourless solution with a pH range of 2.5 to 4.5 when reconstituted in water.
**Molecular Formula:** $C_{66}H_{75}CL_2N_9O_{24}$·HCl
**Molecular Weight:** 1485.74 g/mol
**Structure:**



**CLINICAL PHARMACOLOGY:**
***Mechanism of action:***
In vitro studies indicate that the bactericidal action of vancomycin hydrochloride against many gram-positive bacteria results from the inhibition of cell-wall synthesis. There is also evidence that vancomycin alters the permeability of the cell membrane and selectively inhibits RNA synthesis.

**Pharmacokinetics:**
In subjects with normal kidney function, multiple intravenous dosing of 1 g of vancomycin (15 mg/kg) infused over 60 minutes produces mean plasma concentrations of approximately 63 mcg/mL immediately after the completion of infusion, mean plasma concentrations of approximately 23 mcg/mL 2 hours after infusion, and mean plasma concentrations of approximately 8 mcg/mL 11 hours after the end of the infusion. Multiple dosing of 500 mg infused over 30 minutes produces mean plasma concentrations of about 49 mcg/mL at the completion of infusion, mean plasma concentrations of about 19 mcg/mL 2 hours after infusion, and mean plasma concentrations of about 10 mcg/mL 6 hours after infusion. The plasma concentrations during multiple dosing are like those after a single dose.
***Distribution:***
The volume of distribution ranges from 0.3 to 0.43 L/kg after intravenous administration. Vancomycin is approximately 55% serum protein bound as measured by ultrafiltration at vancomycin serum concentrations of 10 to 100 mcg/mL. After intravenous 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.
***Elimination:***
Mean plasma clearance is about 0.058 L/kg/h, and mean renal clearance is about 0.048 L/kg/h. The mean elimination half-life of vancomycin from plasma is 4 to 6 hours in subjects with normal renal function. In a nephric patients, the mean elimination half-life is 7.5 days. Total body and renal clearance of vancomycin may be reduced in the elderly.
***Metabolism:***
There is no apparent metabolism of the vancomycin.
***Excretion:***
In the first 24 hours after intravenous administration, about 75% of an administered dose of vancomycin is excreted in urine by glomerular filtration. Renal impairment slows excretion of vancomycin. About 60% of an intraperitoneal dose of vancomycin administered during peritoneal dialysis is absorbed systemically in 6 hours. Serum concentrations of about 10 mcg/mL are achieved by intraperitoneal injection of 30 mg/kg of vancomycin. However, the safety and efficacy of the intraperitoneal use of vancomycin has not been established in adequate and well-controlled trials.
***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.
***Resistance:***
Vancomycin is not active in vitro against gram-negative bacilli, mycobacteria, or fungi. There is no cross-resistance between vancomycin and other antibacterials.
***Interaction with other antimicrobials:***
The combination of vancomycin and an aminoglycoside acts synergistically in vitro against many isolates of Staphylococcus aureus, Streptococcus gallolyticus (previously known as Streptococcus bovis), enterococcus spp, and the viridans group streptococci.
***Antimicrobial activity:***
Vancomycin has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections.
***Aerobic gram-Positive bacteria:***
Corynebacterium spp.
Enterococcus spp. (including Enterococcus faecalis)
Staphylococcus aureus (including methicillin-resistant and methicillin-susceptible isolates)
Coagulase negative staphylococci (including S.epidermidis and methicillin-resistant isolates)
Streptococcus gallolyticus (previously known as Streptococcus bovis) Viridans group streptococci.

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for vancomycin against isolates of similar genus or organism group. However, the efficacy of vancomycin in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.
***Aerobic gram-Positive bacteria:***
- Listeria monocytogenes
- Streptococcus pyogenes
- Streptococcus pneumoniae
- Streptococcus agalactiae
- Anaerobic Gram-Positive Bacteria
- Actinomyces species
- Lactobacillus species

**INDICATIONS AND USAGE:**
**1. Septicemia:**
*Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of septicemia due to:*
- Susceptible isolates of methicillin-resistant Staphylococcus aureus (MRSA) and coagulase negative staphylococci.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

**2. Infective endocarditis:**
*Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of infective endocarditis due to:*
- Susceptible isolates of MRSA.
- Viridans group streptococci Streptococcus gallolyticus (previously known as Streptococcus bovis), Enterococcus species and Corynebacterium species. For enterococcal endocarditis, use Vancomycin Hydrochloride for Injection in combination with an aminoglycoside.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.
  Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of early-onset prosthetic valve endocarditis caused by Staphylococcus epidermidis in combination with rifampin and an aminoglycoside.

**3. Skin and skin structure infections:**
*Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of skin and skin structure infections due to:*
- Susceptible isolates of MRSA and coagulase negative staphylococci.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

**4. Bone infections:**
*Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of bone infections due to:*
- Susceptible isolates of MRSA and coagulase negative staphylococci.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

**5. Lower respiratory tract infections:**
Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of lower respiratory tract infections due to:
- Susceptible isolates of MRSA
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

**DRUG INTERACTIONS:**
Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing and anaphylactoid reactions. Concurrent and/or sequential systemic or topical use of other potentially, neurotoxic and/or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymixin B, colistin, viomycin, or cisplatin, when indicated, requires careful monitoring.
***Pregnancy:***
***Teratogenic effects:***
***Pregnancy Category C***
Animal reproduction studies have not been conducted with vancomycin. It is not known whether vancomycin can affect reproduction capacity. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin 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 attributed to the administration of vancomycin. Because the number of patients treated in this study was limited and vancomycin was administered only in the second and third trimesters, it is not known whether vancomycin causes fetal harm. Vancomycin should be given to a pregnant woman only if clearly needed.
***Nursing mothers:***
Vancomycin is excreted in human milk. Caution should be exercised when vancomycin is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
***Pediatric use:***
In pediatric patients, it may be appropriate to confirm desired vancomycin serum concentrations. Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing in pediatric patients (see ADVERSE REACTIONS).
***Geriatric use:***
The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted. Vancomycin dosage schedules should be adjusted in elderly patients.
***Usage precautions:***
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Vancomycin Hydrochloride for Injection and other antibacterial drugs, Vancomycin Hydrochloride for Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**DOSAGE AND ADMINISTRATION:**
***Important administration instructions:***
To reduce the risk of infusion related adverse reactions, administer Vancomycin Hydrochloride for Injection in a diluted solution over 60 minutes or greater. Vancomycin Hydrochloride for Injection concentrations of no more than 5 mg/mL are recommended in adults. In selected patients in need of fluid restriction, a concentration up to 10 mg/mL may be used. Administer Vancomycin Hydrochloride for Injection prior to intravenous anesthetic agents to reduce the risk of infusion related adverse reactions. Administer Vancomycin Hydrochloride by a secure intravenous route of administration to avoid local irritation and phlebitis reactions. The supplied lyophilized powder must be reconstituted and subsequently diluted prior to intravenous use.
***Dosage in adult patients with normal renal function:***
The usual daily intravenous dose is 2 grams divided either as 500 mg every 6 hours or 1 g every 12 hours. Administer each dose over a period of 60 minutes or greater. Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose.

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***Dosage in pediatric patients with normal renal function:***
***Pediatric patients (Aged 1 month and older):***
The usual intravenous dosage of vancomycin is 10 mg/kg per dose given every 6 hours. Each dose should be administered over a period of at least 60 minutes. Close monitoring of serum concentrations of vancomycin may be warranted in these patients.
***Neonates (Up to 1 month old):***
In pediatric patients, up to the age of 1 month, the total daily intravenous dosage may be lower. In neonates, an initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the 1st week of life and every 8 hours thereafter up to the age of 1 month. Each dose should be administered over 60 minutes. In premature infants, vancomycin clearance decreases as postconceptional age decreases. Therefore, longer dosing intervals may be necessary in premature infants. Close monitoring of serum concentrations of vancomycin is recommended in these patients.
***Dosage in patients with renal impairment:***
Dosage adjustment must be made in patients with renal impairment. The initial dose should be no less than 15 mg/kg, in patients with any degree of renal impairment. In premature infants and the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Measure trough vancomycin serum concentrations to guide therapy, especially in seriously ill patients with changing renal function. For functionally anephric patients, an initial dose of 15 mg/kg of body weight should be given to achieve prompt therapeutic serum concentration. A dose of 1.9 mg/kg/24 hr should be given after the initial dose of 15 mg/kg.
***Preparation of vancomycin hydrochloride for injection for intravenous:***
***Administration and storage instructions:***
Vancomycin Hydrochloride for Injection must be reconstituted and further diluted.
***Reconstitution of the lyophilized powder and further dilution:***
At the time of use, reconstitute the vials of Vancomycin Hydrochloride for Injection (lyophilized powder) with Sterile Water for Injection to a concentration of 50 mg of vancomycin/mL then further dilute with an infusion solution to a final concentration of 5 mg/mL (see Table 1 for the appropriate volumes). Discard any reconstituted solution remaining in the vial.

**Volume of Sterile Water for Injection to be Added for Reconstitution and Volume of Infusion Solution to be Used for Further Dilution**

| Vancomycin Strength per Vial | Volume of Sterile Water of Injection for reconstitution | Volume of infusion solution[b] to further dilute to a final concentration of 5 mg/mL |
|---|---|---|
| 250 mg | 5 mL | 50 mL |
| 750 mg | 15 mL | 150 mL |
| 1.25 g | 25 mL | 250 mL |
| 1.5 g | 30 mL | 300 mL |

*After reconstitution, the vials may be stored in a refrigerator for 14 days without significant loss of potency.

Use an infusion solution from the list of the compatible infusion solutions below. The desired dose diluted in this manner should be administered by intermittent IV infusion over a period of 60 minutes or greater. Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard reconstituted and diluted solution 14 days after initial reconstitution.
***Compatibility with intravenous fluids:***
The following diluents are physically and chemically compatible with 5 g/L vancomycin hydrochloride-:
5% Dextrose Injection, USP
5% Dextrose Injection and 0.9% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP
Lactated Ringer's and 5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
***Storage of diluted solutions:***
Solutions that are diluted with 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP 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 Injection and 0.9% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP
Lactated Ringer's and 5% Dextrose Injection, USP
***Incompatibilies for intravenous use:***
Vancomycin solution has a low pH and may cause chemical or physical instability when it is mixed with other compounds.
Mixtures of solutions of vancomycin and beta-lactam antibacterial drugs 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 the administration of these antibacterial drugs. It is also recommended to dilute solutions of vancomycin to 5 mg/mL or less.

**CONTRAINDICATIONS:**
Vancomycin Hydrochloride for Injection is contraindicated in patients with known hypersensitivity to vancomycin.

**WARNINGS AND PRECAUTIONS:**
**1. Infusion reactions:**
Hypotension, including shock and cardiac arrest, wheezing, dyspnea, urticaria, muscular and chest pain may occur with rapid Vancomycin Hydrochloride for Injection administration. The reactions may be more severe in younger patients, particularly children, and in patients receiving concomitant muscle relaxant anesthetics. Rapid intravenous administration of Vancomycin Hydrochloride for Injection may also be associated with "red man syndrome", which manifests as pruritus and erythema that involves the face, neck and upper torso. Infusion-related adverse reactions are related to both the concentration and the rate of administration of vancomycin. Infusion-related adverse reactions may occur, however, at any rate or concentration. Administer Vancomycin Hydrochloride for Injection in a diluted solution over a period of 60 minutes or greater to reduce the risk of infusion-related adverse reactions. In selected patients in need of fluid restriction, a concentration up to 10 mg/mL may be used; use of such higher concentrations may increase the risk of infusion-related adverse reactions. Administer prior to intravenous anesthetic agents when feasible. Stop the infusion if a reaction occurs.
**2. Nephrotoxicity:**
Vancomycin Hydrochloride for Injection can result in acute kidney injury (AKI), including acute renal failure, mainly due to interstitial nephritis or less commonly acute tubular necrosis. AKI is manifested by increasing blood urea nitrogen (BUN) and serum creatinine (Cr). The risk of AKI increases with higher vancomycin serum levels, prolonged exposure, concomitant administration of other nephrotoxic drugs, concomitant administration of piperacillin-tazobactam [see Drug Interactions (7.2)], volume depletion, pre-existing renal impairment and in critically ill patients and patients with co-morbid conditions that predispose to renal impairment. Monitor serum vancomycin concentrations and renal function in all patients receiving Vancomycin Hydrochloride for Injection. More frequent monitoring is recommended in patients with comorbidities that predispose to impairment in renal function or are concomitantly receiving other nephrotoxic drugs, in critically ill patients, in patients with changing renal function, and in patients requiring higher therapeutic vancomycin levels. If acute kidney injury occurs, discontinue Vancomycin Hydrochloride for Injection or reduce the dose.
**3. Ototoxicity:**
Ototoxicity has occurred in patients receiving Vancomycin Hydrochloride for Injection. It may be transient or permanent. Ototoxicity manifests as tinnitus, hearing loss, dizziness or vertigo. The risk is higher in older patients, patients who are receiving higher doses, who have an underlying hearing loss, who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside or who have underlying renal impairment. Monitor for signs and
symptoms of ototoxicity during therapy. Monitor serum vancomycin concentrations and renal function in all patients receiving parenteral vancomycin. Discontinue Vancomycin Hydrochloride for Injection if ototoxicity occurs. Dosage of Vancomycin Hydrochloride for Injection must be adjusted for patients with renal impairment [see Dosage and Administration (2.3)]. Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.
**4. Clostridium Difficile-Associated diarrhea:**
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Vancomycin Hydrochloride for Injection, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated. 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. Prolonged use of Vancomycin Hydrochloride for Injection may result in the overgrowth of nonsusceptible microorganisms. 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 Hydrochloride for Injection.
**5. Hemorrhagic occlusive retinal vasculitis (HORV):**
Hemorrhagic occlusive retinal vasculitis, including permanent loss of vision, occurred in patients receiving intracameral or intravitreal administration of vancomycin during or after cataract surgery. The safety and efficacy of vancomycin administered by the intracameral or the intravitreal route have not been established by adequate and well-controlled trials. Vancomycin is not indicated for the prophylaxis of endophthalmitis.
**6. Neutropenia:**
Reversible neutropenia has been reported in patients receiving Vancomycin Hydrochloride for Injection [see Adverse Reactions (6.1)]. Patients who will undergo prolonged therapy with Vancomycin Hydrochloride for Injection or those who are receiving concomitant drugs which may cause neutropenia should have periodic monitoring of the leukocyte count.
**7. Phlebitis and other administration site reactions:**
Inflammation at the site of injection of Vancomycin Hydrochloride for Injection has been reported. Vancomycin Hydrochloride for Injection is irritating to tissue and must be given by a secure intravenous route of administration to reduce the risk of local irritation and phlebitis. Administration of Vancomycin Hydrochloride for Injection by intramuscular (IM), intraperitoneal, intrathecal (intralumbar or intraventricular), or intravitreal routes has not been approved and is not recommended. The safety and efficacy of vancomycin administered by the intrathecal (intralumbar or intraventricular) route or by the intraperitoneal route have not been established by adequate and well controlled trials. Pain, tenderness, and necrosis occur with IM injection of Vancomycin Hydrochloride for Injection or with inadvertent extravasation. Thrombophlebitis may occur, the frequency and severity of which can be minimized by administering the drug slowly as a dilute solution (2.5 to 5 g/L) and by rotation of venous access sites. Intraperitoneal administration during continuous ambulatory peritoneal dialysis (CAPD) can result in chemical peritonitis. Manifestations range from cloudy dialysate alone to a cloudy dialysate accompanied by variable degrees of abdominal pain and fever. This syndrome appears to be resolve after discontinuation of intraperitoneal vancomycin.
**8. Development of drug-Resistant bacteria:**
Prescribing Vancomycin Hydrochloride for Injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

**ADVERSE REACTIONS:**
***The following clinically significant adverse reactions are described elsewhere in the labeling:***
- Infusion Reactions
- Nephrotoxicity
- Ototoxicity
- Clostridium Difficile-Associated Diarrhea
- Hemorrhagic Occlusive Retinal Vasculitis
- Neutropenia

**OVERDOSAGE:**
Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Hemofiltration and hemoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance.

**INSTRUCTIONS:**
- Store in a cool and dry place, below 30°C.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- Do not freeze.
- Always use freshly reconstituted solution.
- To be sold on the prescription of a registered medical practitioner only.

**PRESENTATION:**
**Cinva Injection 500 mg** : Pack of 500 mg IV injection vial with 10 ml water for injection ampoule.
**Cinva Injection 1 gm** : Pack of 1 gm IV injection vial with 20 ml water for injection ampoule.

**ہدایات:**
دوا کو خشک اور ٹھنڈی جگہ، ۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
منجمد ہونے سے بچائیں۔
انجکشن تیار کرنے کے فوراً بعد استعمال کریں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
NABIQASIM INDUSTRIES (Pvt.) Ltd.
17/24, Korangi Industrial Area, Karachi, Pakistan.

*FOR FURTHER INFORMATION PLEASE CONTACT:*

CCL
Manufactured for:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.

zoom view

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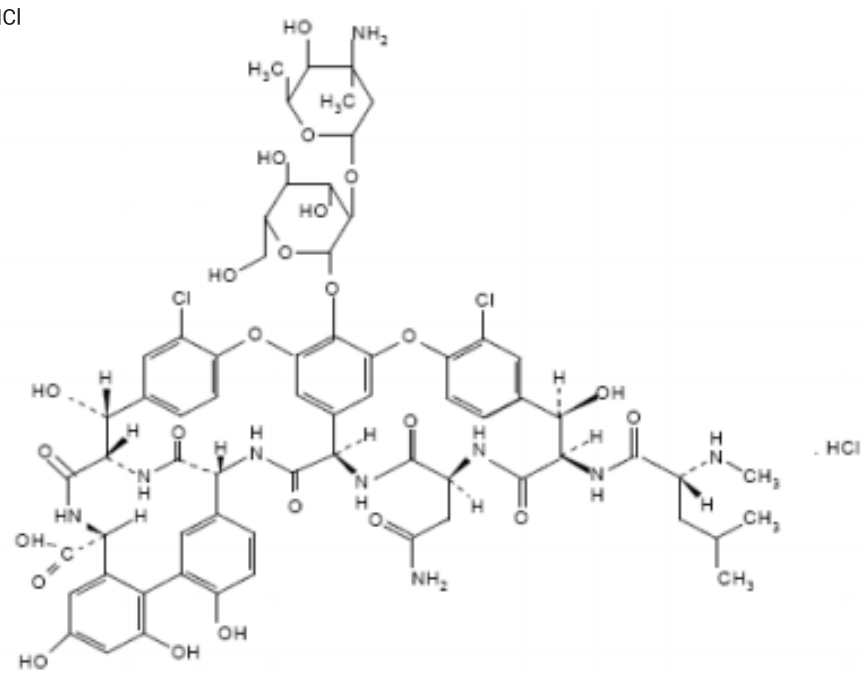

**CLINICAL PHARMACOLOGY:**

***Mechanism of action:***

In vitro studies indicate that the bactericidal action of vancomycin hydrochloride against many gram-positive bacteria results from the inhibition of cell-wall synthesis. There is also evidence that vancomycin alters the permeability of the cell membrane and selectively inhibits RNA synthesis.

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Mean plasma clearance is about 0.058 L/kg/h, and mean renal clearance is about 0.048 L/kg/h. The mean elimination half-life of vancomycin from plasma is 4 to 6 hours in subjects with normal renal function. In a nephric patients, the mean elimination half-life is 7.5 days. Total body and renal clearance of vancomycin may be reduced in the elderly.

***Metabolism:***
There is no apparent metabolism of the vancomycin.
***Excretion:***
In the first 24 hours after intravenous administration, about 75% of an administered dose of vancomycin is excreted in urine by glomerular filtration. Renal impairment slows excretion of vancomycin. About 60% of an intraperitoneal dose of vancomycin administered during peritoneal dialysis is absorbed systemically in 6 hours. Serum concentrations of about 10 mcg/mL are achieved by intraperitoneal injection of 30 mg/kg of vancomycin. However, the safety and efficacy of the intraperitoneal use of vancomycin has not been established in adequate and well-controlled trials.
***Microbiology:***
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***Resistance:***
Vancomycin is not active in vitro against gram-negative bacilli, mycobacteria, or fungi. There is no cross-resistance between vancomycin and other antibacterials.
***Interaction with other antimicrobials:***
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Vancomycin has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections.
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*Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of infective endocarditis due to:*
- Susceptible isolates of MRSA.
- Viridans group streptococci Streptococcus gallolyticus (previously known as Streptococcus bovis), Enterococcus species and Corynebacterium species. For enterococcal endocarditis, use Vancomycin Hydrochloride for Injection in combination with an aminoglycoside.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.
  Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of early-onset prosthetic valve endocarditis caused by Staphylococcus epidermidis in combination with rifampin and an aminoglycoside.

**3. Skin and skin structure infections:**
*Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of skin and skin structure infections due to:*
- Susceptible isolates of MRSA and coagulase negative staphylococci.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

**4. Bone infections:**
*Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of bone infections due to:*
- Susceptible isolates of MRSA and coagulase negative staphylococci.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

**5. Lower respiratory tract infections:**
Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of lower respiratory tract infections due to:
- Susceptible isolates of MRSA
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

**DRUG INTERACTIONS:**
Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing and anaphylactoid reactions. Concurrent and/or sequential systemic or topical use of other potentially, neurotoxic and/or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymixin B, colistin, viomycin, or cisplatin, when indicated, requires careful monitoring.
***Pregnancy:***
***Teratogenic effects:***
***Pregnancy Category C***
Animal reproduction studies have not been conducted with vancomycin. It is not known whether vancomycin can affect reproduction capacity. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin 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 attributed to the administration of vancomycin. Because the number of patients treated in this study was limited and vancomycin was administered only in the second and third trimesters, it is not known whether vancomycin causes fetal harm. Vancomycin should be given to a pregnant woman only if clearly needed.

***Nursing mothers:***
Vancomycin is excreted in human milk. Caution should be exercised when vancomycin is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
***Pediatric use:***
In pediatric patients, it may be appropriate to confirm desired vancomycin serum concentrations. Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing in pediatric patients (see ADVERSE REACTIONS).
***Geriatric use:***
The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted. Vancomycin dosage schedules should be adjusted in elderly patients.
***Usage precautions:***
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Vancomycin Hydrochloride for Injection and other antibacterial drugs, Vancomycin Hydrochloride for Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**DOSAGE AND ADMINISTRATION:**
***Important administration instructions:***
To reduce the risk of infusion related adverse reactions, administer Vancomycin Hydrochloride for Injection in a diluted solution over 60 minutes or greater. Vancomycin Hydrochloride for Injection concentrations of no more than 5 mg/mL are recommended in adults. In selected patients in need of fluid restriction, a concentration up to 10 mg/mL may be used. Administer Vancomycin Hydrochloride for Injection prior to intravenous anesthetic agents to reduce the risk of infusion related adverse reactions. Administer Vancomycin Hydrochloride by a secure intravenous route of administration to avoid local irritation and phlebitis reactions. The supplied lyophilized powder must be reconstituted and subsequently diluted prior to intravenous use.
***Dosage in adult patients with normal renal function:***
The usual daily intravenous dose is 2 grams divided either as 500 mg every 6 hours or 1 g every 12 hours. Administer each dose over a period of 60 minutes or greater. Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose.

***Dosage in pediatric patients with normal renal function:***
***Pediatric patients (Aged 1 month and older):***
The usual intravenous dosage of vancomycin is 10 mg/kg per dose given every 6 hours. Each dose should be administered over a period of at least 60 minutes. Close monitoring of serum concentrations of vancomycin may be warranted in these patients.
***Neonates (Up to 1 month old):***
In pediatric patients, up to the age of 1 month, the total daily intravenous dosage may be lower. In neonates, an initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the 1st week of life and every 8 hours thereafter up to the age of 1 month. Each dose should be administered over 60 minutes. In premature infants, vancomycin clearance decreases as postconceptional age decreases. Therefore, longer dosing intervals may be necessary in premature infants. Close monitoring of serum concentrations of vancomycin is recommended in these patients.
***Dosage in patients with renal impairment:***
Dosage adjustment must be made in patients with renal impairment. The initial dose should be no less than 15 mg/kg, in patients with any degree of renal impairment. In premature infants and the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Measure trough vancomycin serum concentrations to guide therapy, especially in seriously ill patients with changing renal function. For functionally anephric patients, an initial dose of 15 mg/kg of body weight should be given to achieve prompt therapeutic serum concentration. A dose of 1.9 mg/kg/24 hr should be given after the initial dose of 15 mg/kg.
***Preparation of vancomycin hydrochloride for injection for intravenous:***
***Administration and storage instructions:***
Vancomycin Hydrochloride for Injection must be reconstituted and further diluted.
***Reconstitution of the lyophilized powder and further dilution:***
At the time of use, reconstitute the vials of Vancomycin Hydrochloride for Injection (lyophilized powder) with Sterile Water for Injection to a concentration of 50 mg of vancomycin/mL then further dilute with an infusion solution to a final concentration of 5 mg/mL (see Table 1 for the appropriate volumes). Discard any reconstituted solution remaining in the vial.

**Volume of Sterile Water for Injection to be Added for Reconstitution and Volume of Infusion Solution to be Used for Further Dilution**

| Vancomycin Strength per Vial | Volume of Sterile Water of Injection for reconstitution | Volume of infusion solution[b] to further dilute to a final concentration of 5 mg/mL |
|---|---|---|
| 250 mg | 5 mL | 50 mL |
| 750 mg | 15 mL | 150 mL |
| 1.25 g | 25 mL | 250 mL |
| 1.5 g | 30 mL | 300 mL |

*After reconstitution, the vials may be stored in a refrigerator for 14 days without significant loss of potency.

Use an infusion solution from the list of the compatible infusion solutions below. The desired dose diluted in this manner should be administered by intermittent IV infusion over a period of 60 minutes or greater. Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard reconstituted and diluted solution 14 days after initial reconstitution.
***Compatibility with intravenous fluids:***
The following diluents are physically and chemically compatible with 5 g/L vancomycin hydrochloride-:
5% Dextrose Injection, USP
5% Dextrose Injection and 0.9% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP
Lactated Ringer's and 5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
***Storage of diluted solutions:***
Solutions that are diluted with 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP 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 Injection and 0.9% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP
Lactated Ringer's and 5% Dextrose Injection, USP
***Incompatibilies for intravenous use:***
Vancomycin solution has a low pH and may cause chemical or physical instability when it is mixed with other compounds.
Mixtures of solutions of vancomycin and beta-lactam antibacterial drugs 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 the administration of these antibacterial drugs. It is also recommended to dilute solutions of vancomycin to 5 mg/mL or less.

**CONTRAINDICATIONS:**
Vancomycin Hydrochloride for Injection is contraindicated in patients with known hypersensitivity to vancomycin.

**WARNINGS AND PRECAUTIONS:**
**1. Infusion reactions:**
Hypotension, including shock and cardiac arrest, wheezing, dyspnea, urticaria, muscular and chest pain may occur with rapid Vancomycin Hydrochloride for Injection administration. The reactions may be more severe in younger patients, particularly children, and in patients receiving concomitant muscle relaxant anesthetics. Rapid intravenous administration of Vancomycin Hydrochloride for Injection may also be associated with "red man syndrome", which manifests as pruritus and erythema that involves the face, neck and upper torso. Infusion-related adverse reactions are related to both the concentration and the rate of administration of vancomycin. Infusion-related adverse reactions may occur, however, at any rate or concentration. Administer Vancomycin Hydrochloride for Injection in a diluted solution over a period of 60 minutes or greater to reduce the risk of infusion-related adverse reactions. In selected patients in need of fluid restriction, a concentration up to 10 mg/mL may be used; use of such higher concentrations may increase the risk of infusion-related adverse reactions. Administer prior to intravenous anesthetic agents when feasible. Stop the infusion if a reaction occurs.

**2. Nephrotoxicity:**
Vancomycin Hydrochloride for Injection can result in acute kidney injury (AKI), including acute renal failure, mainly due to interstitial nephritis or less commonly acute tubular necrosis. AKI is manifested by increasing blood urea nitrogen (BUN) and serum creatinine (Cr). The risk of AKI increases with higher vancomycin serum levels, prolonged exposure, concomitant administration of other nephrotoxic drugs, concomitant administration of piperacillin-tazobactam [see Drug Interactions (7.2)], volume depletion, pre-existing renal impairment and in critically ill patients and patients with co-morbid conditions that predispose to renal impairment. Monitor serum vancomycin concentrations and renal function in all patients receiving Vancomycin Hydrochloride for Injection. More frequent monitoring is recommended in patients with comorbidities that predispose to impairment in renal function or are concomitantly receiving other nephrotoxic drugs, in critically ill patients, in patients with changing renal function, and in patients requiring higher therapeutic vancomycin levels. If acute kidney injury occurs, discontinue Vancomycin Hydrochloride for Injection or reduce the dose.

**3. Ototoxicity:**
Ototoxicity has occurred in patients receiving Vancomycin Hydrochloride for Injection. It may be transient or permanent. Ototoxicity manifests as tinnitus, hearing loss, dizziness or vertigo. The risk is higher in older patients, patients who are receiving higher doses, who have an underlying hearing loss, who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside or who have underlying renal impairment. Monitor for signs and
symptoms of ototoxicity during therapy. Monitor serum vancomycin concentrations and renal function in all patients receiving parenteral vancomycin. Discontinue Vancomycin Hydrochloride for Injection if ototoxicity occurs. Dosage of Vancomycin Hydrochloride for Injection must be adjusted for patients with renal impairment [see Dosage and Administration (2.3)]. Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.

**4. Clostridium Difficile-Associated diarrhea:**
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Vancomycin Hydrochloride for Injection, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated. 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. Prolonged use of Vancomycin Hydrochloride for Injection may result in the overgrowth of nonsusceptible microorganisms. 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 Hydrochloride for Injection.

**5. Hemorrhagic occlusive retinal vasculitis (HORV):**
Hemorrhagic occlusive retinal vasculitis, including permanent loss of vision, occurred in patients receiving intracameral or intravitreal administration of vancomycin during or after cataract surgery. The safety and efficacy of vancomycin administered by the intracameral or the intravitreal route have not been established by adequate and well-controlled trials. Vancomycin is not indicated for the prophylaxis of endophthalmitis.

**6. Neutropenia:**
Reversible neutropenia has been reported in patients receiving Vancomycin Hydrochloride for Injection [see Adverse Reactions (6.1)]. Patients who will undergo prolonged therapy with Vancomycin Hydrochloride for Injection or those who are receiving concomitant drugs which may cause neutropenia should have periodic monitoring of the leukocyte count.

**7. Phlebitis and other administration site reactions:**
Inflammation at the site of injection of Vancomycin Hydrochloride for Injection has been reported. Vancomycin Hydrochloride for Injection is irritating to tissue and must be given by a secure intravenous route of administration to reduce the risk of local irritation and phlebitis. Administration of Vancomycin Hydrochloride for Injection by intramuscular (IM), intraperitoneal, intrathecal (intralumbar or intraventricular), or intravitreal routes has not been approved and is not recommended. The safety and efficacy of vancomycin administered by the intrathecal (intralumbar or intraventricular) route or by the intraperitoneal route have not been established by adequate and well controlled trials. Pain, tenderness, and necrosis occur with IM injection of Vancomycin Hydrochloride for Injection or with inadvertent extravasation. Thrombophlebitis may occur, the frequency and severity of which can be minimized by administering the drug slowly as a dilute solution (2.5 to 5 g/L) and by rotation of venous access sites. Intraperitoneal administration during continuous ambulatory peritoneal dialysis (CAPD) can result in chemical peritonitis. Manifestations range from cloudy dialysate alone to a cloudy dialysate accompanied by variable degrees of abdominal pain and fever. This syndrome appears to be resolve after discontinuation of intraperitoneal vancomycin.

**8. Development of drug-Resistant bacteria:**
Prescribing Vancomycin Hydrochloride for Injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

**ADVERSE REACTIONS:**
***The following clinically significant adverse reactions are described elsewhere in the labeling:***
- Infusion Reactions
- Nephrotoxicity
- Ototoxicity
- Clostridium Difficile-Associated Diarrhea
- Hemorrhagic Occlusive Retinal Vasculitis
- Neutropenia

**OVERDOSAGE:**
Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Hemofiltration and hemoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance.

**INSTRUCTIONS:**
- Store in a cool and dry place, below 30°C.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- Do not freeze.
- Always use freshly reconstituted solution.
- To be sold on the prescription of a registered medical practitioner only.

**PRESENTATION:**

| | | |
|---|---|---|
| **Cinva Injection 500 mg** | : | Pack of 500 mg IV injection vial with 10 ml water for injection ampoule. |
| **Cinva Injection 1 gm** | : | Pack of 1 gm IV injection vial with 20 ml water for injection ampoule. |

**ہدایات:**

دوا کو خشک اور ٹھنڈی جگہ، ۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

گرمی، دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

منجمند ہونے سے بچائیں۔

انجکشن تیار کرنے کے فوراً بعد استعمال کریں۔

صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
NABIQASIM INDUSTRIES (Pvt.) Ltd.
17/24, Korangi Industrial Area, Karachi, Pakistan.

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