**Ciron Drugs & Pharmaceuticals Pvt. Ltd.** ( Tarapur plant )

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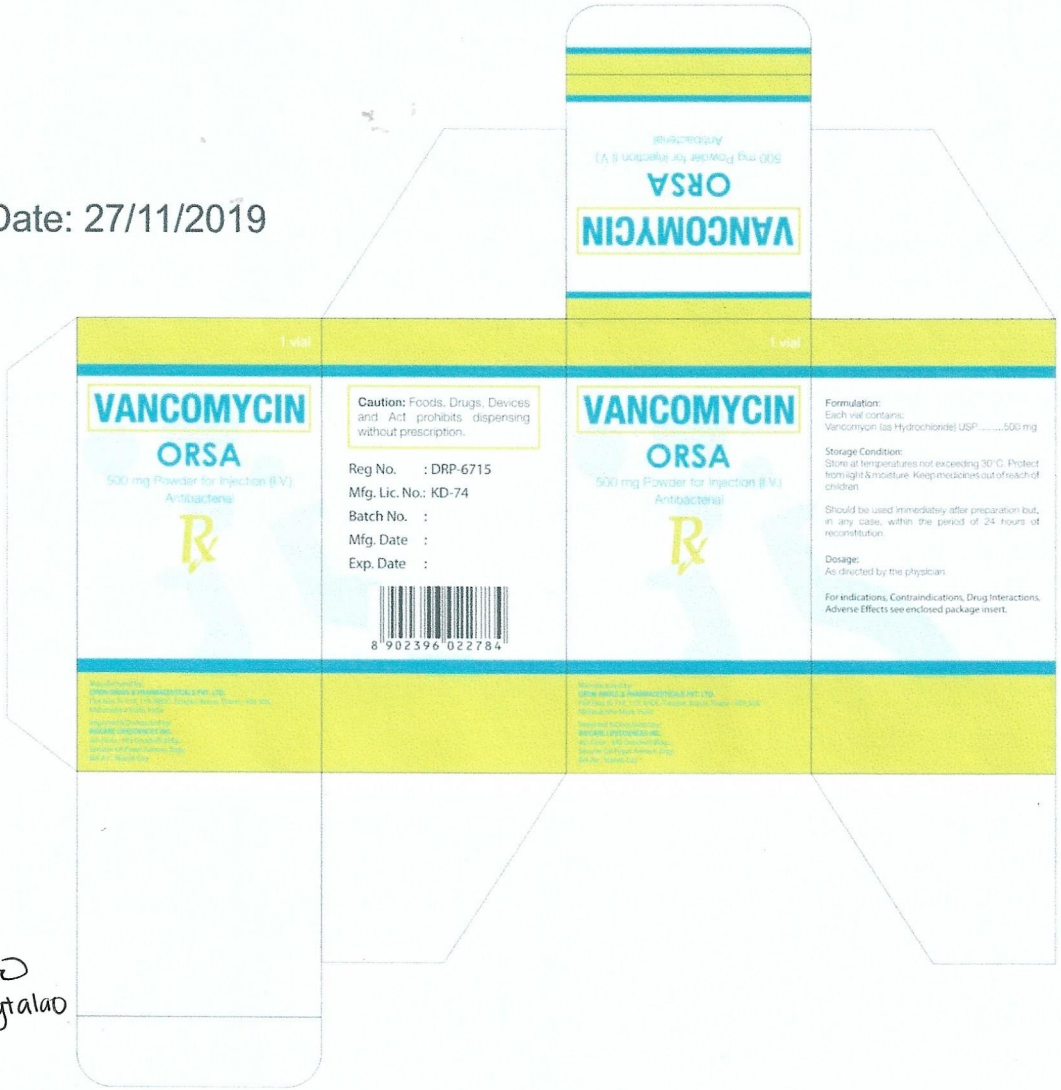
|---|---|---|---|
| Item Description | Carton | Customer / Country | Biocare Lifescience - Phillipines |
| Product Name | Vancomycin injection 500mg | Pack Size | 1 vial |
| Substrate specification | 300 GSM ITC Cyber XL BOARD | Pharmacode / Barcode | N/A |
| Finishing | Aqua Varnish | Dimension | 35 x 35 x 65mm |
| Minimum font size | 4 pt | Artist Name | Arti |
| Colour scheme | Black PANTONE 2296 C | Language | English |
| | PANTONE 7702 C | Date | 26-11-2019 |
| Printer Name | Ambest | | |

Date: 27/11/2019




BIOCARE LIFESCIENCES INC MAKATI PHILS

Approved by:
Hanna Patricia P. Agtalao
10 Mar. 2020

| Prepared By | Reviewed By | | Approved By |
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| PDD | RA | Marketing | QA |
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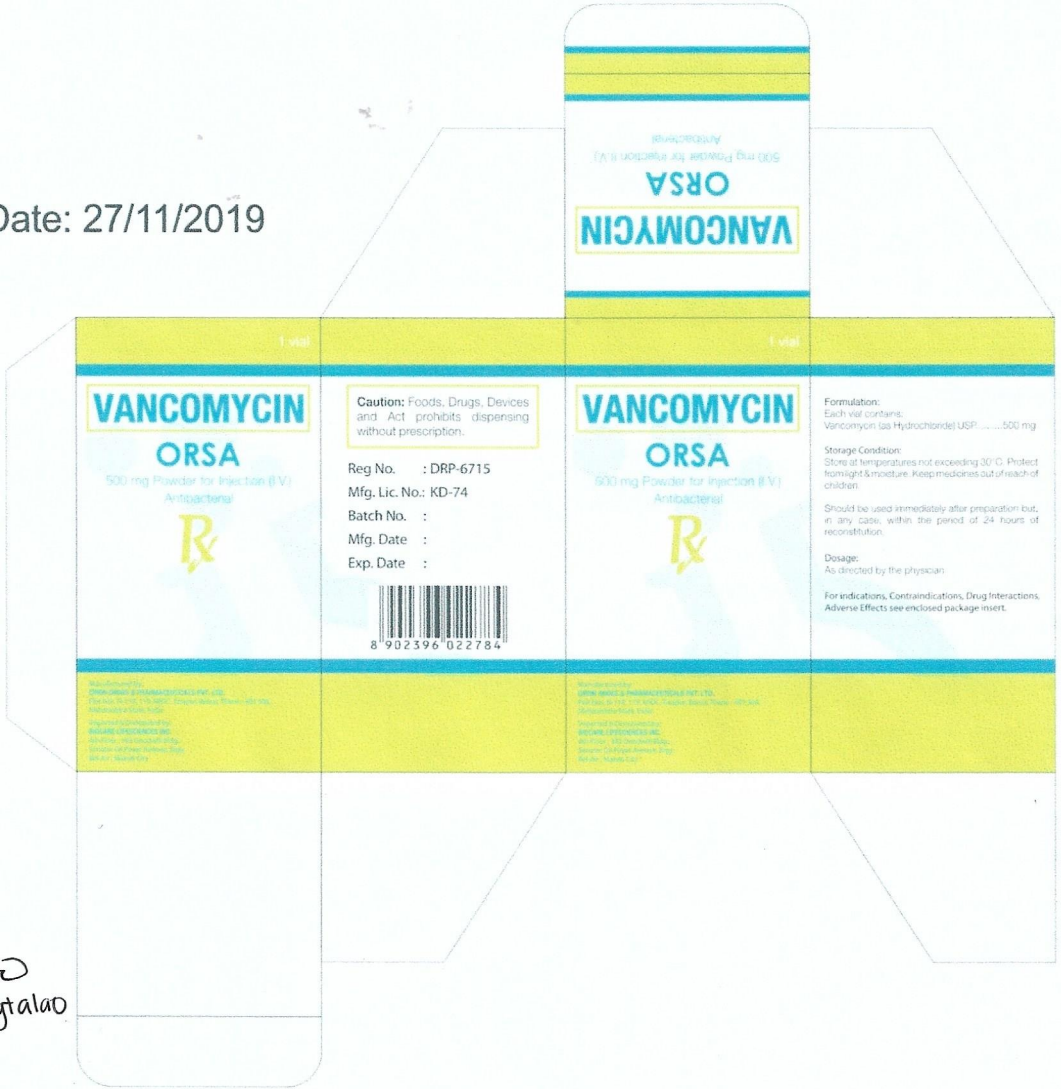


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**Ciron Drugs & Pharmaceuticals Pvt. Ltd.** ( Tarapur plant )

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|---|---|---|---|
| Item Description | Leaflet | Customer / Country | Biocare Lifescience - Phillipines |
| Product Name | Vancomycin injection 500mg | Pack Size | 1 Vial |
| Substrate specification | 60 GSM MAPLITHO Paper | Pharmacode / Barcode | N/A |
| Finishing | N/A | Dimension | 90x165mm |
| Minimum font size | 6 pt | Artist Name | Arti |
| Colour scheme | ■ Black | Language | English |
| | | Date | 26-11-2019 |
| Printer Name | Ambest | | |

Date: 27/11/2019

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# VANCOMYCIN

## ORSA

500 mg Powder for Injection (I.V.)
Antibacterial

**FORMULATION:**
Each vial contains:
Vancomycin
(as Hydrochloride) USP..... 500 mg

**INDICATIONS:**
Vancomycin solution, used intravenously is indicated in the therapy of severe, potentially life-threatening infections due to susceptible gram-positive microorganisms which cannot be treated with or failed to respond to other effective, less toxic antimicrobial medicinal products, such as penicillins and cephalosporins.
Vancomycin should be reserved for those cases where there is a specific indication, to minimize the chance of resistance emerging.
Vancomycin is useful in the treatment of the following severe infections caused by susceptible microorganisms (see Pharmacodoynamics):
- endocarditis,
- infections of bones (osteomyelitis),
- pneumonia,
- soft-tissue infections.

Endocarditis caused by enterococci. Streptococcus viridans or S. bovis should be treated with a combination of vancomycin and an aminoglycoside.
Vancomycin may be used for the perioperative prophylaxis against bacterial endocarditis, in patients at high risk of developing bacterial endocarditis when they undergo major surgical procedures (e.g., cardiac and vascular procedures, etc) and are unable to receive a suitable beta-lactam antibacterial agent.

**DOSAGE AND ADMINISTRATION:**
Vancomycin powder for solution for infusion must be administered intravenously. Each dose should be administered at a rate not exceeding 10 mg/min or over a period of time of at least 60 minutes (whichever is longer).
The dose should be individually adapted according to weight, age and renal function.
The following dosage regimens are recommended:
Patients with normal renal function
Adults and adolescents above 12 years of age:
The recommended daily intravenous dose is 2000 mg, divided into doses of 500 mg every 6 hours or 1000 mg every 12 hours.
For bacterial endocarditis, the generally accepted regimen is 1000 mg vancomycin intravenously every 12 hours for 4 weeks either alone or in combination with other antibiotics (gentamicin plus rifampin, gentamicin, streptomycin). Enterococcal endocarditis is treated for 6 weeks with vancomycin in combination with an aminoglycoside – according to national recommendations.
Peri-operative prophylaxis against bacterial endocarditis: Adults receive 1000 mg vancomycin intravenously prior to surgery (prior to induction of anaesthesia) and depending on time and type of surgery, the dose of 1000 mg of vancomycin i.v. 12 hours postoperatively can be given.
Children one month to 12 years of age:
The recommended intravenous dose is 10 mg/kg, every 6 hours or 20 mg/kg every 12 hours.
Infants and newborns:
The recommended initial dose is 15 mg/kg, followed by 10 mg/kg every 12 hours during the first week of life and every 8 hours after that age and up to 1 month of age. Careful monitoring of serum concentration of vancomycin is recommended (see below).
Elderly patients:
Lower maintenance doses may be required due to the age-related reduction in renal function.
Obese patients:
Modification of the usual daily doses may be required.

Patients with hepatic insufficiency
There is no evidence that the dose has to be reduced in patients with hepatic insufficiency.
Patients with impaired renal function
The dose must be adjusted in patients with impaired renal function. Careful monitoring of serum concentration of vancomycin is recommended.
In patients with mild or moderate renal failure, the starting dose must not be less than 15 mg/kg. In patients with severe renal failure, it is preferable to administer a maintenance dose between 250 mg and 1000 mg at a spacing of several days rather than administer lower daily doses.
Patients with anuria (with practically no renal function) should receive a dose of 15 mg/kg body weight until the therapeutic serum concentration is reached. The maintenance doses are 1.9 mg/kg body weight per 24 hours. In order to facilitate the procedure, adult patients with strongly impaired renal function may obtain a maintenance dose of 250 - 1000 mg at intervals of several days instead of a daily dose.
Dosage in case of haemodialysis
For patients without any renal function, even under regular hemodialysis, the following dosage is also possible:
Saturating dose 1000 mg, maintenance dose 1000 mg every 7 - 10 days.
If polysulfone membranes are used in haemodialysis (high flux dialysis), the half-life of vancomycin is reduced. An additional maintenance dose may be necessary in patients on regular haemodialysis.
Monitoring of vancomycin serum concentrations:
The serum concentration of vancomycin should be monitored at the second day of treatment immediately prior to the next dose, and one hour post infusion. Therapeutic vancomycin blood levels should be between 30 and 40 mg/l (maximum 50 mg/l) one hour after the end of the infusion, the minimum level (short prior to the next administration) between 5 and 10 mg/l.
The concentrations should normally be monitored twice or three times per week.

**Method of administration:**
Parenterally vancomycin shall only be administered as slow intravenous infusion (not more than 10 mg/min – over at least 60 min) which is sufficiently diluted (at least 100 ml per 500 mg or at least 200 ml per 1000 mg).
Patients requiring fluid restriction can receive a solution of 500 mg / 50 ml or 1000 mg / 100 ml. With these higher concentrations the risk for infusion related side effects can be increased.

**Duration of treatment**
The duration of the treatment depends on the severity of the infection as well as on the clinical and bacteriological progress.

**Pharmacological properties**
**Pharmacodynamic properties**
**Mode of action**
Vancomycin is a glycopeptide antibiotic. Vancomycin has a bactericidal effect on proliferating germs by inhibiting the biosynthesis of the cell wall. In addition, it impairs the permeability of the bacterial cell membrane and RNA synthesis.
Mechanism(s) of resistance
Acquired resistance to glycopeptides is based on acquisition of various van gene complexes. Van genes have rarely been found in Staphylococcus aureus, where changes in cell wall structure result in "intermediate" susceptibility, which is most commonly heterogeneous.
There is no cross-resistance between vancomycin and other antibiotics but cross-resistance with other glycopeptide antibiotics, such as teicoplanin, does occur.
Secondary development of resistance during therapy is rare.
In some countries, increasing cases of resistance are observed particularly in enterococci; multi-resistant strains of Enterococcus faecium are especially alarming.
Synergism
The combination of vancomycin with an aminoglycoside antibiotic has a synergistic effect against many strains of Staphylococcus aureus, non-enterococcal 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 indentify the causative organisms and to determine their susceptibility to vancomycin.
Breakpoints
Minimum inhibitory concentration (MIC) breakpoint established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Staphylococcus spp. and Streptococcus spp.are Susceptible =< 2 mg/L and Resistant > 2 mg/L; for Enterococcus spp. are Susceptible =< 4 mg/L and Resistant > 4 mg/L; and for non-species related are Susceptible =< 2 mg/L and Resistant > 4 mg/L.
Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent is at least some types of infections is questionable.
Vancomycin has a narrow spectrum of action.

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| **Commonly susceptible species** |
| Staphylococcus spp |
| Streptococcus pneumoniae |
| Streptococcus spp |
| Corynebacterium spp |
| Enterococcus spp |
| **Species for which acquired resistance may be a problem** |
| Enterococcus faecium |
| **Inherently resistant organisms** |
| Gram-negative bacteria, mycobacteria, fungi |

**Pharmacokinetic properties**
• Distribution: Following intravenous administration, vancomycin is distributed to almost all tissues and diffuses in pleural, pericardial, ascitic and synovial fluid as well as in the cardiac muscle and in heart valves. Comparable high concentrations are achieved as in blood plasma. Data about the vancomycin concentrations in bone (spongiosa, compacta) vary widely. The apparent distribution volume in steady state is stated to be 0.43 (up to 0.9) L/kg. In non-inflamed meninges vancomycin passes the blood-brain barrier only to a low extent. Vancomycin is bound to plasma proteins at 30 to 55 % and even higher.
• **Elimination**: Vancomycin is metabolized only to a low extent. After parenteral administration it is excreted almost completely as microbiologically active substance (approx. 75-90% within 24 hours) through glomerular filtration via the kidneys. Biliary excretion is insignificant (less than 5% of a dose).
In patients with normal renal function, the half-life in serum is about 4-6 (5-11) hours, in children 2.2-3 hours. In impaired renal function, the half-life of vancomycin may be considerably prolonged (up to 7.5 days). Due to ototoxicity of vancomycin therapy-adjuvant monitoring of the plasma concentrations is indicated in such cases.
Mean plasma concentrations after i.v. infusion of 1000 mg vancomycin over 60 minutes were about 63 mg/L at the end of the infusion, about 23 mg/L after 2 hours and about 8 mg/L after 11 hours.
The clearance of vancomycin from plasma correlates nearly with the glomerular filtration rate.
The total systemic and renal clearance of vancomycin can be reduced in elderly patients.
As studies in anephric patients showed, the metabolic clearance seems to be very low.
No vancomycin metabolites have been identified so far in humans.
If vancomycin is given during a peritoneal dialysis via the intraperitoneal route, approx. 60% reaches the systemic circulation during 6 hours. After i.p. administration of 30 mg/kg BW, serum levels of approx. 10 mg/l are achieved.
In case of oral use, high-polar vancomycin is virtually not absorbed. It appears after oral administration in active form in the stool, and is therefore a suitable chemotherapeutic for pseudomembranous colitis and staphylococcal colitis.

Vancomycin diffuses readily across the placenta and is distributed into cord blood.

**CONTRAINDICATIONS:**
Hypersensitivity to vancomycin

**DRUG INTERACTIONS:**
Other potentially nephrotoxic or ototoxic medications
Concurrent or sequential administration of vancomycin with other potentially neurotoxic or/and nephrotoxic active substances particularly gentamycin, amphotericin B, streptomycin, neomycin, kanamycin, amikacin, tobramycin, viomycin, bacitracin, polymyxin B, colistin and cisplatin may potentiate the nephrotoxicity and/or ototoxicity of vancomycin and consequently requires careful monitoring of the patient.
Because of synergic action (e.g. with gentamycin) in these cases the maximum dose of vancomycin has to be restricted to 500 mg every 8 hours.
Anaesthetics
Concurrent administration of vancomycin and anaesthetic agents has been associated with erythema, histamine like flushing and anaphylactoid reactions. This may be reduced if the vancomycin is administered over 60 minutes before anaesthetic induction.
Muscle relaxants
If vancomycin is administered during or directly after surgery, the effect (neuromuscular blockade) of muscle relaxants (such as succinylcholine) concurrently used can be enhanced and prolonged.

**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.

**ADVERSE EFFECTS:**
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
The adverse reactions listed below is defined using the 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).
The most common adverse reactions are phlebitis and pseudo-allergic reactions in connection with too rapid intravenous use of vancomycin.
Blood and the lymphatic system disorders
Rare (≥ 10,000 to < 1/1,000): thrombocytopenia, neutropenia, agranulocytosis, eosinophilia.
Immune system disorders
Rare (≥ 10,000 to < 1/1,000): anaphylactic reactions, hypersensitivity reactions.
Ear and labyrinth disorders
Uncommon (≥ 1,000 to < 1/1.00): transient or permanent loss of hearing.
Rare (≥ 10,000 to < 1/1,000): tinnitus, dizziness.
Cardiac disorders
Very rare (< 1/10,000): cardiac arrest.
Vascular disorders
Common (>1/100 to < 1/10): decrease in blood pressure, thrombophlebitis.
Rare (≥ 10,000 to < 1/1,000): vasculitis.
Respiratory, thoracic and mediastinal disorders
Common (>1/100 to < 1/10): dyspnoea, stridor.
Gastrointestinal disorders
Rare (≥ 10,000 to < 1/1,000): nausea.
Very rare(< 1/10,000): pseudomembranous enterocolitis
Skin and subcutaneous tissue disorders

Common (>1/100 to < 1/10): exanthema and mucosal inflammation, pruritus, urticaria.
Very rare (< 1/10, 000): exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome, IgA induced bullous dermatitis.
Renal and urinary disorders
Common (>1/100 to < 1/10): renal insufficiency manifested primarily by increased serum creatinine or serum urea concentrations.
Rare (≥ 10,000 to < 1/1,000): interstitial nephritis, acute renal failure.
General disorders and administration site conditions
Common (>1/100 to < 1/10): redness of the upper body and the face, pain and spasm of the chest and back muscles.
Rare (≥ 10,000 to < 1/1,000): drug fever, shivering.
During or shortly after rapid infusion anaphylactic reactions may occur. The reactions abate when administration is stopped, generally between 20 minutes and 2 hours after having stopped administration.
Ototoxicity has primarily been reported in patients given high doses, or concomitant treatment with other ototoxic medicinal products, or with pre-existing reduction in kidney function or hearing.

**Special warnings and Precautions for use**
Preparation of the reconstituted solution
Dissolve Vancomycin 500 mg Powder for solution for infusion in 10 ml of sterile Water for injection.
One ml of reconstituted solution contains 50 mg of vancomycin.
Appearance of reconstituted solution
After reconstitution the solution is clear and colorless to slightly yellowish brown without visible particles.
For storage conditions of the reconstituted medicinal product, see section 6.3
Preparation of final diluted Solution for infusion
Reconstituted solutions containing 50 mg/ml of vancomycin should be further diluted.
Suitable diluents are:
5% Glucose Injection or
0.9% Sodium Chloride Injection or
5% Glucose Injection with 0.9% Sodium Chloride Injection
Intermittent infusion:
Reconstituted solution containing 500 mg of vancomycin (50 mg/ml) must be diluted further with at least 100 ml diluent (to 5mg/ml).
The concentration of vancomycin in Solution for infusion should not exceed 5 mg/ml.
The desired dose should be administered slowly by intravenous use at a rate of no more than 10 mg/minute, for at least 60 minutes or even longer.
Continuous infusion:
This should be used only if treatment with an intermittent infusion is not possible. Dilute 1000 mg to 2000 mg of dissolved vancomycin in a sufficient amount of the above suitable diluent and administer it in the form of a drip infusion, so that the patient will receive the prescribed daily dose in 24 hours.
Appearance of diluted solution
After dilution the solution is clear and colorless without visible particles.
For storage conditions of the diluted medicinal product, see section 6.3.
Before administration, the reconstituted and diluted solutions should be inspected visually for particulate matter and discoloration. Only clear, and colorless solution free from particles should be used.

**Incompatibilities**
Vancomycin solutions have a low pH value. This may lead to chemical or physical instability if mixed with other substances. Therefore, each parenteral solution should be checked visually for precipitations and discolouration prior to use.
This medicinal product must not be mixed with other medicinal products except those mentioned in Special precautions for disposal and other handling.
Combination therapy
In case of combination therapy of vancomycin with other antibiotics/chemotherapeutics, the preparations should be administered separately.
Mixtures of solutions of vancomycin and beta-lactam antibiotics have been shown to be physically incompatible. The likelihood of precipitation increases with higher concentrations of vancomycin. It is recommended to adequately flush the intravenous lines between administration of these antibiotics. It is also recommended to dilute solutions of vancomycin to 5 mg/mL or less.

**Special precautions for disposal and other handling**
The product must be reconstituted and the resulting concentrate must then be diluted prior to use.
Preparation of the reconstituted solution
Dissolve Vancomycin 500 mg Powder for solution for infusion in 10 ml of sterile Water for injection.
One ml of reconstituted solution contains 50 mg of vancomycin.
Appearance of reconstituted solution
After reconstitution the solution is clear and colorless to slightly yellowish brown without visible particles.
Appearance of diluted solution
After dilution the solution is clear and colorless without visible particles.

**Disposal**
Vials are for single use only. Unused medicinal products must be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**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 period.
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 other antibiotics have failed. 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 should to stop breastfeeding should be considered.

**Effects on ability to drive and use machines**
Vancomycin has no or negligible influence on the ability to drive and use machines.

**Caution:**
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

**STORAGE:**
Store at temperature not exceeding 30°C. Protect from light & moisture.
Keep all medicines out of reach of children.

**AVAILABILITY:** Flint, USP type III Glass vials with grey butyl rubber plugs, aluminium seal and green flip-off cap x 10 mL (box of 1's).

**Reg. No.: DRP-6715**

**Date of first authorisation/renewal of the authorization**
14 June 2016

Manufactured by:
**CIRON DRUGS & PHARMACEUTICALS PVT. LTD.**
Plot Nos. N-118, 119, MIDC, Tarapur, Boisar,
Thane - 401 506, Maharashtra State, India.

Imported & Distributed by:
**BIOCARE LIFESCIENCES INC.**
4th Floor , 393 Goodwill Bldg.,
Senator Gil Puyat Ave. Brgy.
Bel-Air , Makati City.

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