VANTOX - CP
(Vancomycin Hydrochloride for Injection USP 1gm)

1.4.1 Prescribing Information

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT:
VANTOX- CP (Vancomycin Hydrochloride for Injection USP 1 gm/vial)

1.1 Strength:
1 gm

1.2 Pharmaceutical form:
Powder for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Batch Size: 10000 Vials

Ingredients	Specifications	Mg/vial	Quantity for Batch	Reason or Purpose for inclusion
Active Ingredients				
Vancomycin HCl Eq to Vancomycin	USP	1025 (A*) 1000	10.00 Kg	Active Pharmaceutical Ingredient

Note : (A*) : Quantity varies as per potency of raw material.

q. s. : Quantity Sufficient

3. PHARMACEUTICAL FORM:

Powder for Injection

Visual Description:
White, almost white or tan to brown free flowing powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indication(s)

Vancomycin is useful in therapy of severe staphylococcal (including methicillin resistant staphylococcal) infections in patients who cannot receive or who have failed to respond to the penicillins and cephalosporins or who have infections with staphylococci that are resistant to other antibiotics.

Vancomycin is effective alone or in combination with an aminoglycoside for endocarditis caused by Strep. viridans or Strep. bovis. For endocarditis caused by enterococci (eg Strep. faecalis),vancomycin is effective only in combination with an aminoglycoside. Vancomycin is effective for the treatment of diphtheroid.

The effectiveness of vancomycin has been documented in other infections due to staphylococci including osteomyelitis, pneumonia, septicaemia and, skin and skin structure infections. When staphylococcal infections are localised and purulent, antibiotics are used as adjuncts to appropriate surgical measures.

Vancomycin should be administered orally for the treatment of staphylococcal enterocolitis and antibiotic associated pseudomembranous colitis (produced by C difficile). Parenteral administration of vancomycin alone is inappropriate for this indication. Vancomycin is not effective by the oral route for other types of infections. For oral administration the parenteral formulation may be used. Some systemic absorption may occur following oral administration in patients with pseudo – membranous colitis.

4.2 Posology and method of administration

Adults

The usual intravenous dose is 500 milligrams every 6 hours or 1 g every 12 hours. A 500 milligram dose of vancomycin should be infused over a period of at least 60 minutes, whereas a 1g dose should be administered over a period of at least two hours. Vancomycin must not be given by intramuscular injections.

Adults with impaired renal function and the elderly

In the elderly, dosage reduction may be necessary to a greater extent than expected because of decreasing renal function. Measurement of vancomycin serum concentrations is required to optimise therapy, especially in seriously ill patients with changing renal function.

For most patients with renal impairment or the elderly, the dosage calculations may be made by using the following table. The vancomycin dose per day in milligrams is about 15 times the glomerular filtration rate in mL/minute (See table below).

Vancomycin Dosage in patients with impaired renal function

Creatinine Clearance ml/min	Vancomycin Hydrochloride Dose milligram/24h
100	1545
90	1390
80	1235
70	1080
60	925
50	770
40	620
30	465
20	310
10	155

Loading dose

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

Anephric patients

The table is not valid for functionally anephric patients. For such patients, an initial dose of 15 milligrams/kg bodyweight should be given in order to promptly achieve therapeutic serum concentrations. The dose required to maintain stable concentrations is 1.9 milligrams/kg/24 hours. Since individual maintenance doses of 250 (250,000 IU) - 1,000 (1000,000 IU) milligrams are convenient, in patients with marked renal impairment, a dose may be given every several days rather than on a daily basis. In anuria, a dose of 1,000 milligrams every seven to ten days has been recommended.

The majority of patients with infections caused by organisms susceptible to the antibiotic show a therapeutic response by 48 - 72 hours. The total duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. In staphylococcal endocarditis, therapy for three weeks or longer is recommended.

Children
The paediatric dosage of vancomycin is calculated on the basis of 10 milligrams/kg bodyweight every six hours after an initial loading dose of 15 milligrams/kg. Each dose should be administered over a period of at least 60 minutes.

Infants and neonates
In neonates and young infants, the total daily intravenous dosage may be lower. An initial dose of 15 milligrams/kg is suggested, followed by 10 milligrams/kg every twelve hours in the first week of life and every eight hours thereafter until one month of age. Close monitoring of serum vancomycin concentrations is mandatory in these patients. Each dose should be administered over a period of at least 60 minutes.

Oral administration
The usual adult total daily dosage for antibiotic associated pseudo – membranous colitis produced by C difficile is 500 milligrams to 2 g given in three or four divided doses for 7 to 10 days. The total daily dosage in children is 40 milligrams/kg bodyweight in three or four divided doses. The total daily dosage should not exceed 2 g.
The contents of 1 vial (500 milligrams) (500,000 IU) may be diluted in 30 mL of distilled or deionised water and given to the patient to drink, or the diluted material may be administered via nasogastric tube. Common flavouring syrups may be added to the solution to improve the taste for oral administration.

Preparation & Stability: At the time of use, reconstitute by adding 10 ml of Sterile Water for Injection to the 500 mg vial. Vials reconstituted in this manner will give a solution of 50 mg/ml.
Further Dilution is required : After reconstitution with Sterile Water for Injection, 5% Dextrose Injection, or 0.9% Sodium Chloride for Injection, the vials may be stored in a refrigerator for 14 days without significant loss of potency. Reconstituted solutions containing 500 mg of Vancomycin must be diluted with atleast 100 ml of diluent. The desired dose, diluted in this manner, should be administered by intermittent intravenous infusion over a period of atleast 60 minutes.

4.3 Contraindications:
Vancomycin is contraindicated in patients with known hypersensitivity to this drug.

4.4 Special warnings and precautions for use:
Vancomycin Hydrochloride for Intravenous Infusion should be administered in a dilute solution at a rate not exceeding 500 milligrams/hour to avoid rapidinfusion – related reactions, e.g. hypotension, flushing, erythema, urticaria and pruritus. Stopping the infusion usually results in a prompt cessation of these reactions.
When given intravenously, toxic serum levels can occur. Vancomycin is excreted fairly rapidly by the kidney and blood levels increase markedly with decreased renal clearance. During parenteral therapy, the risk of toxicity and nephrotoxicity appears appreciably increased by high blood concentrations or prolonged treatment.
Because of its nephrotoxicity, vancomycin should be used with care in patients with renal insufficiency. If it is necessary to use vancomycin parenterally in patients with renal impairment, the dose and/or dose intervals should be adjusted carefully and blood levels monitored. Serial monitoring of renal function should be performed.
Vancomycin should be avoided (if possible) in patients with previous hearing loss. If it is used in such patients, the dose of vancomycin should be regulated by periodic determination of drug levels in the blood. Patients with renal insufficiency and individuals over the age of 60 should be given serial tests of auditory function and of vancomycin blood levels. All patients receiving the drug should have periodic hematologic studies, urinalyses, and liver and renal function tests.

Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of oral vancomycin and, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of vancomycin. The risk is greater if renal impairment is present.

It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly.

Reversible neutropenia has been reported in patients receiving Vancomycin Hydrochloride. Patients who will undergo prolonged therapy with vancomycin or those who are receiving concomitant drugs which may cause neutropenia should have periodic monitoring of the leukocyte count.

Since vancomycin is irritating to tissue and causes drug fever, pain and possibly necrosis it should never be injected intramuscularly; it must be administered intravenously. Pain and thrombophlebitis occur in many patients receiving vancomycin and are occasionally severe.

The safety and efficacy of vancomycin administration by the intrathecal (intralumbar or intraventricular) route have not been assessed.

Reports have revealed that administration of sterile vancomycin HCl by the intraperitoneal route during continuous ambulatory peritoneal dialysis (CAPD) has resulted in a syndrome of chemical peritonitis. This syndrome appears to be short lived after discontinuation of intraperitoneal vancomycin.

If parenteral and oral vancomycin are administered concomitantly an additive effect can occur. This should be taken into consideration when calculating the total dose. In this situation serum levels of the antibiotic should be monitored.

In surgical patients the administration of vancomycin should be carefully timed in relation to the induction of anaesthesia.

The use of vancomycin may result in overgrowth of nonsusceptible organisms. If new infections due to bacteria or fungi appear during therapy with this product, appropriate measures should be taken including withdrawal of vancomycin. Patients taking oral vancomycin should be warned of its offensive taste.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration with other neurotoxic or nephrotoxic drugs, eg. streptomycin, neomycin, gentamicin, kanamycin, amikacin, amphotericin B, bacitracin, tobramycin, polymyxin B, colistin and cisplatin requires careful monitoring.

Diuretics such as ethacrynic acid and frusemide may aggravate to toxicity.

Cholestyramine has been shown to bind vancomycin *in-vitro*. Therefore, if oral vancomycin is used with cholestyramine, the two drugs should be administered several hours apart.

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 the administration of these antibiotics.

Reversible neutropenia has been reported in patients receiving Vancomycin Hydrochloride. Patients who are receiving concomitant drugs which may cause neutropenia should have periodic monitoring of the leukocyte count.

There have been reports that the frequency of infusion related events (including hypotension, flushing, erythema, urticaria, and pruritus) increases with the concomitant administration of anaesthetic agents.

Vancomycin may enhance neuromuscular blockade produced by drugs such as suxamethonium or vecuronium.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation:

Vancomycin Hydrochloride for Intravenous Infusion should be given to a pregnant woman only if clearly needed.

4.7 Effects on ability to drive and use machines:

Not available

4.8 Undesirable effects:

Infusion related events: During or soon after infusion of vancomycin, patients may develop anaphylactoid reactions including hypotension, palpitations, substernal pressure, tachycardia, wheezing, dyspnoea, urticaria, or pruritus.

Auditory and vestibular: Sensorineural deafness which may be accompanied by tinnitus has occurred but the incidence is low. Permanent deafness is more likely to occur in patients with compromised auditory or renal function but reversible deafness has been reported in normal patients. Vertigo and dizziness have also been reported.

Cardiovascular: Hypotension, palpitations, substernal pressure, tachycardia.

Dermatological: Pruritus at injection site, generalised flushing, erythematous macular rash with intense pruritus over face, neck and upper body have occurred after too rapid injection of the drug. Tissue irritation and necrosis occurs after intramuscular injection or extravasation from the intravenous site.

Gastrointestinal: Oral doses are extremely unpalatable. In leukaemic patients, oral dosing regimens are associated with frequent nausea, diarrhoea and occasional vomiting.

Haematological: Some patients have been reported to have developed reversible neutropenia, usually starting one week or more after onset of therapy with Vancomycin or after a total dose of more than 25 grams. Neutropenia appears to be promptly reversible when vancomycin is discontinued.

Immunological: Hypersensitivity reactions with chills, nausea, urticaria, macular rash, fever and rigors.

4.13 Overdose

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is not effectively removed by either haemodialysis or peritoneal dialysis. Haemofiltration and heamoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance.

In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

ATC Code(s): J01XA01

Pharmacotherapeutic group: Glycopeptide antibacterials

Vancomycin is a biological material, described as a tricyclic glycopeptide obtained from cultures of *Nocardiaorientalis (Streptomyces orientalis)*. Vancomycin is present as the hydrochloride salt for parenteral administration. The drug is not absorbed from the gastrointestinal tract, and an aqueous solution of the product can be administered orally in the treatment of pseudomembranous colitis.

Vancomycin is a bactericidal antibiotic and appears to bind to the bacterial cell wall causing blockage of glycopeptide polymerisation. This effect produces immediate inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane. It is active against many gram

positive organisms including staphylococci, group A beta haemolytic streptococci, S*treptococcus pneumoniae*, enterococci, corynebacterium and clostridium species. It does not demonstrate clinical efficacy against gram negative bacteria, fungi or yeasts, and hence the product literature only indicates use in severe infections caused by gram positive organisms.

5.2 Pharmacokinetic properties:

Vancomycin is poorly absorbed by mouth. An intravenous dose of 1 g produces serum levels averaging 25 microgram per ml after two hours in patients with normal renal function. Serum levels are higher in patients with renal impairment and toxicity may result. Vancomycin is excreted unchanged in the urine, at least 80% is excreted in the first 24 hours. It has a half-life of about 6 hours in patients with normal renal function. In patients on haemodialysis the serum half-life of vancomycin ranges from 120 to 216 hours.

Vancomycin readily diffuses into pleural, pericardial, ascitic and synovial fluids. It does not diffuse into cerebrospinal fluid with normal meninges, but therapeutic concentrations may be reached in patients with acute meningitis. Vancomycin is active against many gram-positive organisms including *Clostridium difficile*. Gram-negative bacteria, mycobacteria and fungi are highly resistant. Many strains of gram-positive bacteria are sensitive *in-vitro* to vancomycin concentrations of 0.5 to 5 microgram/ml, but a few *Staphlococcus aureus* strains require 10-20 microgram/ml for inhibition.

5.3 Preclinical safety data

Not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Not Applicable

6.2 Incompatibilities:

Vancomycin solution has a low pH that may cause chemical or physical instability when it is mixed with other compounds. Chemically incompatible with dexamethasone sodium phosphate, Heparin sodium, methicillin sodium, phenobarbitone sodium, sodium bicarbonate.

6.3 Shelf life:

24 months from the date of manufacture.

6.4 Special precautions for storage:

Store at a temperature not exceeding 25°C. Protect from light. Do not freeze.

6.5 Nature and contents of container:

Vantox-CP (Vancomycin Hydrochloride for Injection) is supplied in a single dose 20ml glass vial containing Vancomycin 1gm powder for reconstitution.

6.6 Special precautions for disposal and other handling:

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESS:

Samarth Life Sciences Pvt. Ltd.

Unit II, Plot No. 2, Industrial Area,

Lodhimajra, Baddi, Dist. Solan,
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8. MARKETING AUTHORISATION NUMBERS
Not applicable

9. DATE OF FIRST REGISTRATION /RENEWAL OF THE REGISTRATION
Not applicable

10.DATE OF REVISION OF THE TEXT
Not applicable

11.DOSIMETRY (IF APPLICABLE)
Not applicable

12.INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
Not applicable