SUMMARY OF PRODUCTS CHARACTERISTICS

1. Name of the Medicinal Product

Vancomycin Hydrochloride for Injection USP 500 mg

1.1 Product Name

Vanco 500

1.2 Strength

500 mg/ vial

1.3 Pharmaceutical Dosage Form

Powder for Infusion

2. Qualitative and Quantitative Composition

2.1 Qualitative Declaration

Vancomycin Hydrochloride for Injection USP 500 mg

2.2 Quantitative Declaration

Each Vial contains:

Sterile Vancomycin Hydrochloride USP

Equivalent to Vancomycin…..... 500 mg

3. Pharmaceutical Form

Powder for Infusion

4. Clinical Particulars

4.1 Therapeutic Indications

Vancomycin is an amphoteric glycopeptide antimicrobial substance produced by the growth of certain strains of Nocardia Orientalis (formerly known as Strepromyces orientalis). It is bactericidal against many gram-positive organisms.

Vancomycin is indicated in potentially life-threatening infections due to susceptible gram-positive organisms which cannot be treated by other effective, less toxic antimicrobial drugs, such as the penicillins and cephalosporins. As vancomycin is an antibiotic to which nearly all strains of staphylococcus remain susceptible, it should be reserved for those cases where there is a specific indication, to minimise the chance of resistance emerging. Vancomycin is one of the agents of choice in treating methicillin resistant staphylococcal infection.

Staphylococcal Infections

Vancomycin is useful in therapy of severe 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 including methicillin. Vancomycin has been used successfully alone in the treatment of staphylococcal endocarditis and as prophylaxis against endocarditis in patients at risk from dental or surgical procedures**.**

Its efficacy has been documented in other infections due to staphylococci, including osteomyelitis, pneumonia, septicemia and soft tissue infections.

Pseudomembranous Colitis and staphylococcal enterocolitis

Since vancomycin is not absorbed from the gastrointestinal tract, oral vancomycin is indicated for severe cases of antibiotic-associated pseudomembranous colitis (usually involving Clostridium difficile) and staphylococcal enterocolitis. Relapse of pseudomembranous colitis is possible and usually occurs 4 to 21 days after vancomycin is discontinued. Patients appear to respond to a second course of oral vancomycin.

Intravenous vancomycin is ineffective for these indications.

Vancomycin is not effective by the oral route for other types of infection. Intravenous administration may be used concomitantly if required.

4.2 Posology and Method of Administration

For intravenous infusion and oral use only and not for intramuscular administration.

Adults

Intravenous

The usual adult intravenous dose is 500 mg every six hours or 1 g every twelve hours**,** in Sodium Chloride 0.9% solution, Dextrose 5%. Each dose should be administered at no greater than 10 mg/min.

Staphylococcal infections normally respond within 48-72 hours. Duration of therapy depends on type and severity of infections and patient response. For bacterial endocarditis, the generally accepted regimen is 500 mg vancomycin intravenously every six hours for a minimum of three weeks either alone or in combination with other antibiotics.

Therapeutic range of serum levels:

Following multiple intravenous doses, peak serum concentrations, measured 2 hours after infusion is complete, range from 18-26 mg/litre. Trough levels measured immediately prior to the next dose should be 5-10 mg/litre. Ototoxicity has been associated with serum drug levels of 80-100 mg/litre, but this is rarely seen when serum levels are kept at or below 30 mg/litre.

Paediatric:

Intravenous:

The usual intravenous dosage is 10 mg/kg per dose given every 6 hours (total daily dosage 40 mg/kg of body weight). Each dose should be administered over a period of at least 60 minutes. In neonates and young infants, the total daily dosage may be lower. An initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours in the first week of life and every 8 hours thereafter until one month of age. Close monitoring of serum vancomycin concentrations may be warranted in these patients.

Geriatric:

Because of its ototoxicity and nephrotoxicity, vancomycin should be used with caution in patients with renal insufficiency or previous hearing loss. The elderly are particularly at risk. Doses should be titrated on the basis of serum levels. Blood levels should be monitored and renal function tests performed regularly. The elderly are particularly susceptible to auditory damage and should be given serial tests for auditory function if over the age of 60. Concurrent or sequential use of other neurotoxic substances should be avoided. (See special warnings and precautions for these).

With impaired renal function

In patients with impaired renal function, dosage regimen of vancomycin must be modified in response to degree of renal impairment, severity of infection, susceptibility of causative organism and serum concentrations of the drug. A suggested starting dose in patients with impaired renal function is 15 mg/kg with subsequent doses based mainly on renal function and serum concentrations of the drug.

Accumulation of the drug may occur with prolonged therapy and regular monitoring of serum levels should be carried out. The following guide is provided. This data is not valid for functionally anephric patients on dialysis

Creatinine Clearance ml/min/kg	Vancomycin Dose mg/kg/24 hrs
2.0	30.9
1.5	23.2
1.0	15.4
0.5	7.7
0.2	3.1

In anephric patients, a loading dose of 15 mg/kg body weight should be given with subsequent dosage of 1.9 mg/kg/24hrs. Since individual maintenance doses of 250 mg -1 g 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 1g every 7-10 days has been recommended**.**

In patients on haemodialysis, the drug is not significantly removed by haemodialysis. A dose of 1 g of vancomycin every seven days produces effective blood levels. Serum levels should be monitored to avoid drug accumulation and resultant toxicity. The serum half-life ranges from 120 to 216 hours.

In patients undergoing peritoneal dialysis, the half-life of vancomycin has been reported at around 18 hours. To prevent undue lowering of serum levels during peritoneal dialysis, an additional amount of vancomycin could be added to the dialysate in a concentration of 25 microgram per ml.

Preparation of Solution:

At the time of use, add 10 ml of sterile Water for Injections BP to a 500 mg vial of Vancomycin Hydrochloride 500 mg Powder for Concentrate for Infusion. Similarly, add 20 ml of sterile Water for Injections BP to a 1 g vial of Vancomycin Hydrochloride 1 g Powder for Concentrate for Infusion. Vials reconstituted in this manner will give a solution of 50 mg/ml. Further dilution is required depending on method of administration:

(i) Intermittent infusion (the preferred method of administration):

Reconstituted solutions containing 500 mg vancomycin must be diluted with at least 100 ml diluent. Reconstituted solutions containing 1 g vancomycin must be diluted with at least 200 ml diluent.

Sodium Chloride Intravenous Infusion B.P. or Dextrose Intravenous Infusion B.P. are suitable diluents. The desired dose should be administered by intravenous infusion at a rate of no more than 10 mg/min. If administered over a shorter period of time or in higher concentrations, there is a possibility of inducing marked hypotension in addition to thrombophlebitis. Rapid administration may also produce flushing and a transient rash over the neck and shoulders.

(ii) Continuous infusion (should only be used when intermittent infusion not feasible):

1 g or 2 g of vancomycin may be added to a sufficiently large volume of Sodium Chloride 0.9% Injection or Glucose 5% in Water for Injection to permit the desired dose to be infused over twenty-four hours.

4.3 Contraindications

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

4.4 Special Warnings and Precautions for use

Warnings

Complications of occasional severe hypotension (including shock and rare cardiac arrest), histamine like responses and maculopapular or erythematous rash ("red man's syndrome" or "red neck syndrome") are thought to be related to the rate of the infusion. Vancomycin should be infused in a dilute solution at a rate not greater than 10 mg/min to avoid rapid infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions. Slow infusions over one hour are recommended for infants and children.

Because of its toxicity and nephrotoxicity, vancomycin should be used with care in patients with renal impairment. The risk of toxicity is increased by high blood concentrations or prolonged therapy. Therefore, blood levels should be monitored and dosage adjusted if it is necessary to use vancomycin in such patients.

The concurrent or sequential use of other nephrotoxic drugs requires careful monitoring and should be avoided if possible.

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

Vancomycin should, if possible, be avoided in patients with previous hearing loss. Serial testing of auditory function in those aged more than 60 years is advised. If used it is very important that the dose be adjusted by monitoring the blood concentrations of the drug. Deafness may be preceded by tinnitus. The elderly are more susceptible to auditory damage. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment.

Precautions

Vancomycin is very irritating to tissue and causes injection site necrosis if injected intramuscularly. Pain and thrombophlebitis occur in many patients receiving vancomycin and are occasionally severe. The frequency and severity of thrombophlebitis can be minimised if the drug is administered as a dilute solution (2.5-5 mg/ml) of Dextrose 5% or Normal Saline 0.9% solution and if the sites of injection are changed regularly.

All patients receiving vancomycin should have periodic haematological studies, urine analysis, liver and renal function tests.

Anaesthetic induced myocardial depression may be enhanced by vancomycin. During anaesthesia, doses must be well diluted and administered slowly with close cardiac monitoring. Position changes should be delayed until the infusion is completed to allow for postural adjustment.

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 of vancomycin and anaesthetic agents has been associated with erythema, histamine like flushing and anaphylactoid reactions.

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

Diuretics such as ethacrynic acid and frusemide may aggravate ototoxicity.

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.

4.6 Pregnancy and Lactation

Use in Pregnancy

Teratology studies have been performed at 5 times the human dose in rats and 3 times the human dose in rabbits, and have revealed no evidence of harm to the foetus due to vancomycin. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin hydrochloride on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin hydrochloride 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 attributable to vancomycin. Because vancomycin was administered only in the second and third trimesters, it is not known whether it causes foetal harm. Vancomycin should be given in pregnancy only if clearly needed and blood levels should be monitored carefully to minimise the risk of foetal toxicity. It has been reported, however, that pregnant patients may require significantly increased doses of vancomycin to achieve therapeutic serum concentrations.

Use in Lactation:

Vancomycin Hydrochloride is excreted in breast milk but it is not known whether it is harmful to the newborn. Therefore, it is not recommended for nursing mothers unless the expected benefits outweigh any potential risk.

4.7 Effects on ability to Drive and use Machines

None stated.

4.8 Undesirable Effects

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 been reported rarely.

Cardiovascular:

Hypotension, palpitations, substernal pressure, phlebitis, rare cases of vasculitis, and tachycardia. (All effects due to excessively rapid infusion or insufficient dilution of drug.)

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 IM injection or extravasation from IV site. Vancomycin has been associated with the bullous eruption disorders, rashes including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis and linear IgA bullous dermatosis. If a bullous disorder is suspected, the drug should be discontinued and specialist dermatological assessment should be carried out.

Gastrointestinal:

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

General:

The use of vancomycin may result in overgrowth of non-susceptible organisms resulting in new bacterial or fungal infections.

Genitourinary:

Transient elevations of urea and granular casts in the urine occasionally occur. Nephrotoxicity in the presence of normal renal function at therapeutic serum levels is rare. Rare cases of interstitial nephritis have been reported.

Haematological:

Reversible neutropenia, usually starting one week or more after onset of intravenous therapy or after a total dose of more than 25 g. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has been rarely reported. Reversible agranulocytosis (less than 500 granulocytes per mm^3) has been reported rarely, although causality has not been established. Eosinophilia has been reported.

Immunological:

Histamine release with chills, nausea, urticaria, macular rash, fever and rigors, even at normal doses but usually following rapid drug administration. Anaphylactoid reactions, hypersensitivity reactions and anaphylaxis have been reported.

Ocular:

Subconjunctival injections have infrequently been used in the treatment of bacterial corneal ulcers but may cause severe inflammation or sloughing.

Miscellaneous:

Pain and muscle spasm of the chest and back.

4.9 Overdose

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed from the blood by haemodialysis or peritoneal dialysis. Haemoperfusion with Amberlite resin XAD-4 has been reported to be of limited benefit.

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

Vancomycin is a biological material, described as a tricyclic glycopeptide obtained from cultures of Nocardia orientalis (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, Streptococcus 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.

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.

6. Pharmaceutical Particulars

6.1 List of Excipient(S)

There are no excipients used in this product.

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

Vancomycin Hydrochloride for Injection USP 500 mg has a shelf life of 3 years.

6.4 Special Precautions for Storage

Store below 30°C in a dry place. Protect from light.

6.5 Nature and contents of Container

Available in Plain glass vial (USP Type-I).

6.6 Special precautions for Disposal and Other Handling

For single use. Discard any unused contents.

7. Marketing Authorisation holder

SWISS PARENTERALS LTD
809, Kerala Industrial Estate,
G.I.D.C, Nr, Bavla, Dist.
Ahmedabad-382 220. Gujarat, India.

8. Marketing Authorisation number

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9. Date of first Authorisation / Renewal of the Authorisation

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10. Date of Revision / Approval of the text

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11. Legal Category

Prescription only medicine