SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vancomycin 1g Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains vancomycin 1 g (equivalent to 1 000 000 IU) as vancomycin hydrochloride

For full list of excipients, see 6.1

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

Powder for solution for oral use

A whitish porous cake

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vancomycin is indicated in potentially life-threatening infections which cannot be treated with other effective, less toxic antimicrobial drugs, including the penicillins and cephalosporins.

Vancomycin is useful in the 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 resistant to other antibiotics.

Vancomycin is used in the treatment of endocarditis and as prophylaxis against endocarditis in patients at risk from dental or surgical procedures.

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

Vancomycin may be used orally for the treatment of staphylococcal enterocolitis and pseudomembranous colitis due to *Clostridium difficile*. Parenteral administration of vancomycin is not effective for these indications. 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. (see section 6.6 for full preparation instructions).

Infusion-related adverse events are related to both concentration and rate of administration of vancomycin.

Concentrations of no more than 5mg/ml are recommended. In selected patients in need of fluid restriction, a concentration up to 10mg/ml may be used; use of such higher concentrations may increase the risk of infusion-related events. Infusions

should be given over at least 60 minutes. In adults, if doses exceeding 500mg are used, a rate of infusion of no more than 10mg/min is recommended. Infusion-related events may occur, however, at any rate or concentration.

Intravenous infusion in patients with normal renal function

Adults: The usual intravenous dose is 500mg every six hours or 1g every 12 hours, in Sodium Chloride Intravenous Infusion BP or 5% Dextrose Intravenous Infusion BP. Each dose should be administered at no more than 10mg/min. Other patient factors, such as age, obesity or pregnancy, may call for modification of the usual daily dose. The majority of patients with infections caused by organisms sensitive to the antibiotic show a therapeutic response within 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, treatment for three weeks or longer is recommended.

Pregnancy: It has been reported that significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant patients, but see 'Warnings'.

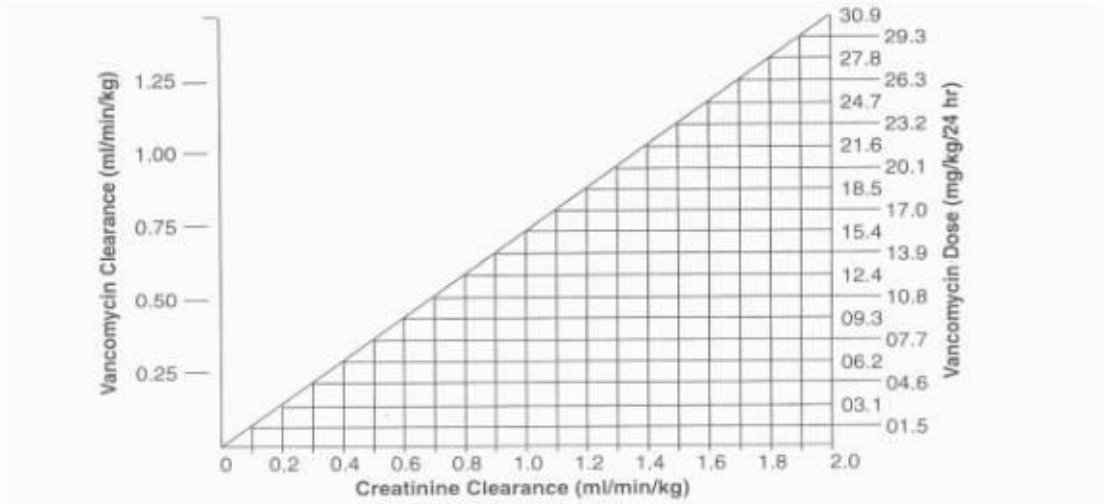
The elderly: Dosage reduction may be necessary to a greater extent than expected because of decreasing renal function (see below). Monitor auditory function - see 'Warnings' and 'Precautions'.

Children: The usual intravenous dosage is 10mg/kg per dose given every 6 hours (total daily dosage 40mg/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 15mg/kg is suggested, followed by 10mg/kg every 12 hours in the first week of life and every 8 hours thereafter until one month of age. Each dose should be administered over 60 minutes. Close monitoring of serum vancomycin concentrations may be warranted in these patients.

Patients with impaired renal function

Dosage adjustments must be made to avoid toxic serum levels. In premature infants and the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Regular monitoring of serum levels is advised in such patients, as accumulation has been reported, especially after prolonged therapy. Vancomycin serum concentrations may be determined by use of a microbiological assay, radioimmunoassay, fluorescence polarisation immunoassay, fluorescence immunoassay or high-pressure liquid chromatography. The following nomogram based on creatinine clearance values, is provided:



Dosage nomogram for vancomycin in patients with impaired renal function

The nomogram is not valid for functionally anephric patients on dialysis. For such patients, a loading dose of 15mg/kg body weight should be given to achieve therapeutic serum levels promptly, and the dose required to maintain stable levels is 1.9mg/kg/24 hours. Since individual maintenance doses of 250mg to 1g 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 to 10 days has been recommended.

Preparation of solutions: See 'Instructions for use/handling'.

Measurement of serum concentrations

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

Oral administration

The contents of vials for parenteral administration may be used.

Adults and the elderly: The usual daily dose given is 500mg in divided doses for 7 to 10 days, although up to 2g/day have been used in severe cases. The total daily dosage should not exceed 2g. Each dose may be reconstituted in 30ml water and either given to the patient to drink, or administered by nasogastric tube.

Children: The usual daily dose is 40mg/kg in three or four divided doses for 7 to 10 days. The total daily dosage should not exceed 2g.

Common flavouring syrups may be added to the solution at the time of administration to improve the taste.

4.3 Contraindications

Hypersensitivity to vancomycin

4.4 Special warnings and precautions for use

Warnings:

Rapid bolus administration (eg, over several minutes) may be associated with exaggerated hypotension, including shock, and, rarely, cardiac arrest. Vancomycin should be infused in a dilute solution over a period of not less than 60 minutes to avoid rapid infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions (see 'Posology and method of administration' and 'Undesirable effects' sections).

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.

Due to its potential ototoxicity and nephrotoxicity, vancomycin should be used with care in patients with renal insufficiency and the dose should be reduced according to the degree of renal impairment. The risk of toxicity is appreciably increased by high blood concentrations or prolonged therapy. Blood levels should be monitored and renal function tests should be performed regularly.

Vancomycin should also be avoided in patients with previous hearing loss. If it is used in such patients, the dose should be regulated, if possible, by periodic determination of the drug level in the blood. 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.

Usage in paediatrics: In premature neonates and young infants, it may be appropriate to confirm desired vancomycin serum concentrations. Concomitant administration of vancomycin and anaesthetic agents has been associated with erythema and histamine-like flushing in children.

Usage in the elderly: The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted (see 'Posology and method of administration').

Precautions:

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. Therefore, monitoring of serum concentrations may be appropriate in these patients.

Patients with borderline renal function 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 haematological studies, urine analysis and renal function tests.

Vancomycin is very irritating to tissue, and causes injection site necrosis when injected intramuscularly; it must be infused intravenously. Injection site pain and thrombophlebitis occur in many patients receiving vancomycin and are occasionally severe.

The frequency and severity of thrombophlebitis can be minimised by administering the drug slowly as a dilute solution (2.5 to 5.0g/l) and by rotating the sites of infusion.

Prolonged use of vancomycin may result in the overgrowth of non-susceptible organisms. 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

There have been reports that the frequency of infusion-related events increases with the concomitant administration of anaesthetic agents. Infusion-related events may be minimised by the administration of vancomycin as a 60-minute infusion prior to anaesthetic induction.

Concurrent or sequential systemic or topical use of other potentially neurotoxic or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymixin B, colistin, viomycin or cisplatin, when indicated, requires careful monitoring.

4.6 Fertility, pregnancy and lactation

Usage 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.

Usage in nursing mothers: Vancomycin hydrochloride is excreted in human milk. Caution should be exercised when vancomycin is administered to a nursing woman. It is unlikely that a nursing infant can absorb a significant amount of vancomycin from its gastro-intestinal tract.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Infusion-related events: During or soon after rapid infusion of vancomycin, patients may develop anaphylactoid reactions including hypotension, wheezing, dyspnoea, urticaria or pruritus. Rapid infusion may also cause flushing of the upper-body ('red-neck syndrome') or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours. In animal studies, hypotension and bradycardia occurred in animals given large doses of vancomycin at high concentrations and rates. Such events are infrequent if vancomycin is given by slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when vancomycin was administered at a rate of 10mg/min or less.

Nephrotoxicity: Rarely, renal failure, principally manifested by increased serum creatinine or blood urea concentrations, have been observed, especially in patients given large doses of intravenously administered vancomycin. Rare cases of interstitial nephritis have been reported. Most occurred in patients who were given aminoglycosides concomitantly or who had pre-existing kidney dysfunction. When vancomycin was discontinued, azotaemia resolved in most patients.

Ototoxicity: Hearing loss associated with intravenously administered vancomycin has been reported. Most of these patients had kidney dysfunction, pre-existing hearing loss, or concomitant treatment with an ototoxic drug. Vertigo, dizziness and tinnitus have been reported rarely.

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

Miscellaneous: Phlebitis, hypersensitivity reactions, anaphylaxis, nausea, chills, drug fever, eosinophilia, rashes (including exfoliative dermatitis) and rare cases of vasculitis. Vancomycin has been associated with the bullous eruption disorders 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.

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 Pharmacodynamic properties

Pharmacotherapeutic group: Glycopeptide antibacterials

ATC code: J01XA01

Vancomycin is a glycopeptide antibiotic derived from *Nocardia orientalis* (formerly *Streptomyces orientalis*), and is active against many Gram-positive bacteria, including *Staphylococcus aureus, Staph. epidermidis*, alpha and beta haemolytic streptococci, group D streptococci, corynebacteria and clostridia.

5.2 Pharmacokinetic properties

Vancomycin is not significantly absorbed from the normal gastro-intestinal tract and is therefore not effective by the oral route for infections other than staphylococcal enterocolitis and pseudomembranous colitis due to *Clostridium difficile*.

5.3 Preclinical safety data

Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of vancomycin was found in standard laboratory tests. No definitive fertility studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Vancomycin solution has a low pH that may cause chemical or physical instability when it is mixed with other compounds.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

24 months

Reconstituted solution intended for parenteral administration

Physical and chemical stability have been demonstrated for a period of 24 hours when stored at 2 to 8ºC.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

Prior to administration, parenteral drug products should be inspected visually for particulate matter and discolouration whenever solution or container permits.

Reconstituted solution intended for oral administration

Solution intended for oral administration may be stored in a refrigerator (2 to 8ºC) for up to 24 hours.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original closed pack

Please see section 6.3 for storage of the reconstituted solution.

6.5 Nature and contents of container

Type II transparent glass vial, with rubber closure type 1.

Vancomycin 1g powder for infusion is available in packs of 1 vial.

6.6 Special precautions for disposal

Prior to administration, parenteral drug products should be inspected visually for particulate matter and discolouration whenever solution or container permits.

Preparation of solution: At the time of use add 20ml of Water for Injections Ph.Eur to the vial. Vials reconstituted in this manner will give a solution of 50mg/ml.

After reconstitution the solution should be clear and free of particles.

FURTHER DILUTION IS REQUIRED. Read instructions which follow:

1. *Intermittent infusion* is the preferred method of administration. Reconstituted solutions must be diluted with at least 200ml diluent. Sodium Chloride Intravenous Infusion BP or 5% Dextrose Intravenous Infusion BP are suitable diluents. The desired dose should be given by intravenous infusion over a period of at least 60 minutes. If administered over a shorter period of time or in higher concentrations, there is the possibility of inducing marked hypotension in addition to thrombophlebitis. Rapid administration may also produce flushing and a transient rash over the neck and shoulders.

2. *Continuous infusion* (should be used only when intermittent infusion is not feasible). 1-2g can be added to a sufficiently large volume of Sodium Chloride Intravenous Infusion BP or 5% Dextrose Intravenous Infusion BP to permit the desired daily dose to be administered slowly by intravenous drip over a 24 hour period.

3. Oral administration

The contents of vials for parenteral administration may be used.

Common flavouring syrups may be added to the solution at the time of administration to improve the taste.

The vials are for single use only. Please discard any remaining solution immediately after use.

7 MARKETING AUTHORISATION HOLDER

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08970 Sant Joan Despi, Barcelona, Spain

8 MARKETING AUTHORISATION NUMBER(S)

04584/06757/NMR/2018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Aug 28, 2020

10 DATE OF REVISION OF THE TEXT