Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

VANBACT 500mg I.V. Injection

2. Qualitative and quantitative composition

Each vial of lyophilized powder contains:
Vancomycin Hydrochloride USP
Eq. to Vancomycin..... 500mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Injection.
Light tan colored powder/cake

4. Clinical particulars

4.1 Therapeutic indications

Vancomycin Hydrochloride is indicated for the treatment of serious or severe infections caused by susceptible strains of Methicillin Resistant (β-lactam resistant) Staphylococci.
It is indicated for penicillin-allergic patients who cannot receive or who have failed to respond to other drugs including the penicillins or cephalosporins and for infections caused by Vancomycin susceptible organisms that are resistant to other antimicrobial drugs. \Vancomycin Hydrochloride is indicated for initial therapy when Methicillin Resistant Staphylococci are suspected but after susceptibility data are available, therapy should be adjusted accordingly.
Vancomycin Hydrochloride is effective in the treatment of Staphylococcal endocarditis.
Its effectiveness has been documented in other infections caused by Staphylococci including septicemia, bone infections, lower respiratory tract infections and skin and skin structure infections.

4.2 Posology and method of administration

Patients with Normal Renal Function:
Adults: The usual daily intravenous dose is 2g divided either as 500mg every 6 hours or 1g every 12 hours. Each dose should be administered over a period of at least 60 minutes. Other patient factors such as age or obesity may call for modification of the usual daily dose.
Children: The total daily intravenous dosage of Vancomycin Hydrochloride, calculated on the basis of 40mg/kg of body weight, can be divided and incorporated into the child's 24 hours fluid requirement. 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. In both neonates and infants; an initial dose of 15mg/kg is suggested, followed by 10mg/kg every 12 hours for neonates in the first week of life and every 8 hours thereafter up to the age of 1 month.

Close monitoring of serum concentrations of Vancomycin Hydrochloride may be warranted in these patients.
The safety and efficacy of Vancomycin Hydrochloride administration by the intrathecal (intra-lumbar or intraventricular) route have not been assessed.
Patients with impaired Renal function and elderly patients: Dosage adjustment must be made in patients with impaired renal function. In the elderly, dosage reduction may be necessary to a greater extent than expected because of decreasing renal function.
Measurement of Vancomycin serum concentration can be helpful in optimizing therapy, especially in seriously ill patients with changing renal function. Vancomycin serum concentration can be determined by use of microbiological assay, radioimmunoassay, fluorescence polarization immunoassay, fluorescence immunoassay or high-pressure liquid chromatography.
The dosage of Vancomycin Hydrochloride per day in mg is about 15 times the glomerular filtration rate in ml/min.
The initial dose should be not less than 15mg/kg, even in patients with mild to moderate renal insufficiency. For functionally anephric patients, an initial dose of 15mg/kg of body weight should be given in order to achieve prompt therapeutic serum concentrations.
The dose required to maintain stable concentrations is 1.9mg/kg/24 hours. Since individual maintenance dose of 250 to 1,000mg is convenient, 1 dose may be given every several days rather than on a daily basis, in patients with marked renal impairment, in anuria, a dose of 1,000mg every 7 to 10 days has been recommended.
Intermittent infusion is the recommended method of administration. Intraperitoneal administration is not recommended.
Preparation and Stability:
At the time of use, reconstitute by adding either 10ml of Sterile water for injection to the 500mg vial or 20ml of Sterile water for injection to the 1g vial of dry sterile Vancomycin Hydrochloride powder.
Further Dilution: After reconstitution, the vial may be stored in a refrigerator for 14 days without significant loss of potency. Reconstituted solution containing 500mg of Vancomycin must be diluted with at least 100ml of diluent. Reconstituted solution containing 1g of Vancomycin Hydrochloride must be diluted with at least 200ml of diluent. The desired dose, diluted in the manner, should be administered by intermittent intravenous infusion over a period of at least 60 minutes.
Compatibility with other Drugs and Intravenous Fluids: Solutions that are diluted with 5% Dextrose injection or 0.9% Sodium Chloride injection 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, Lactated Ringer's Injection, Lactated Ringers and 5% Dextrose Injection, Normosol-M and 5% Dextrose Isolyte E. Vancomycin Hydrochloride solution have a low pH and may cause physical instability of other compounds. Parenteral drug products should be inspected visually for particulate matter and discolorations prior to administration whenever solution or container permits.

4.3 Contraindications

Known hypersensitivity to Vancomycin Hydrochloride.
Vancomycin should not be administered intramuscularly due to the risk of necrosis at the site of administration.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions are possible (see sections 4.3 and 4.8). In case of hypersensitivity reactions, treatment with vancomycin must be discontinued immediately and the adequate emergency measures must be initiated.
In patients receiving vancomycin over a longer-term period or concurrently with other medications which may cause neutropenia or agranulocytosis, the leukocyte count should be monitored at regular intervals. All patients receiving vancomycin should have periodic hematologic studies, urine analysis, liver and renal function tests.
Vancomycin should be used with caution in patients with allergic reactions to teicoplanin, since cross hypersensitivity, including fatal anaphylactic shock, may occur.

Spectrum of antibacterial activity

Vancomycin has a spectrum of antibacterial activity limited to Gram-positive organisms. It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a high suspicion that the most likely pathogen(s) would be suitable for treatment with vancomycin.
The rational use of vancomycin should take into account the bacterial spectrum of activity, the safety profile and the suitability of standard antibacterial therapy to treat the individual patient.

Ototoxicity

Ototoxicity, which may be transitory or permanent (see section 4.8) has been reported in patients with prior deafness, who have received excessive intravenous doses, or who receive concomitant treatment with another ototoxic active substance such as an aminoglycoside. Vancomycin should also be avoided in patients with previous hearing loss. Deafness may be preceded by tinnitus. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment. To reduce the risk of ototoxicity, blood levels should be determined periodically and periodic testing of auditory function is recommended.
The elderly are particularly susceptible to auditory damage. Monitoring of vestibular and auditory function in the elderly should be carried out during and after treatment. Concurrent or sequential use of other ototoxic substances should be avoided.

Infusion-related reactions

Rapid bolus administration (i.e. over several minutes) may be associated with exaggerated hypotension (including shock and, rarely, cardiac arrest), histamine like responses and maculopapular or erythematous rash (“red man's syndrome” or “red neck syndrome”). Vancomycin should

be infused slowly in a dilute solution (2.5 to 5.0 mg/ml) at a rate no greater than 10 mg/min and over a period not less than 60 minutes to avoid rapid infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions.
The frequency of infusion-related reactions (hypotension, flushing, erythema, urticaria and pruritus) increases with the concomitant administration of anesthetic agents (see section 4.5). This may be reduced by administering vancomycin by infusion over at least 60 minutes, before anesthetic induction.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with vancomycin treatment (see section 4.8). Most of these reactions occurred within a few days and up to eight weeks after commencing treatment with vancomycin.
At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, vancomycin should be withdrawn immediately and an alternative treatment considered. If the patient has developed a SCAR with the use of vancomycin, treatment with vancomycin must not be restarted at any time.

Administration site related reactions

Pain and thrombophlebitis may occur in many patients' receiving intravenous vancomycin and are occasionally severe. The frequency and severity of thrombophlebitis can be minimized by administering the medicinal product slowly as a dilute solution (see section 4.2) and by changing the sites of infusion regularly.
The efficacy and safety of vancomycin have not been established for the intrathecal, intra-lumbar and intraventricular routes of administration.

Parental administration

Nephrotoxicity

Vancomycin should be used with care in patients with renal insufficiency, including anuria, as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations. The risk of toxicity is increased by high blood concentrations or prolonged therapy. Regular monitoring of the blood levels of vancomycin is indicated in high dose therapy and longer-term use, particularly in patients with renal dysfunction or impaired faculty of hearing as well as in concurrent administration of nephrotoxic or ototoxic substances, respectively (see sections 4.2 and 4.5)

Eye disorders

Vancomycin is not authorized for intracameral or intravitreal use, including prophylaxis of endophthalmitis.
Hemorrhagic occlusive retinal vasculitis (HORV), including permanent loss of vision, have been observed in individual cases following intracameral or intravitreal use of vancomycin during or after cataract surgery.

Oral administration
Intravenous administration of vancomycin is not effective for the treatment of *Clostridium difficile* infection. Vancomycin should be administered orally for this indication.
Testing for *Clostridium difficile* colonization or toxin is not recommended in children younger than 1 year due to high rate of asymptomatic colonization unless severe diarrhea is present in infants with risk factors for stasis such as Hirschsprung disease, operated anal atresia or other severe motility disorders. Alternative aetiologies should always be sought and *Clostridium difficile* enterocolitis be proven.
Potential for Systemic Absorption
Absorption may be enhanced in patients with inflammatory disorders of the intestinal mucosa or with *Clostridium difficile*-induced pseudomembranous colitis. These patients may be at risk for the development of adverse reactions, especially if there is a concomitant renal impairment. The greater the renal impairment, the greater the risk of developing the adverse reactions associated with the parenteral administration of vancomycin. Monitoring of serum vancomycin concentrations of patients with inflammatory disorders of the intestinal mucosa should be performed.
Nephrotoxicity
Serial monitoring of renal function should be performed when treating patients with underlying renal dysfunction or patients receiving concomitant therapy with an aminoglycoside or other nephrotoxic drugs.
Ototoxicity
Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity in patients with an underlying hearing loss, or who are receiving concomitant therapy with an ototoxic agent such as an aminoglycoside.
Drug interactions with anti-motility agents and proton pump inhibitors
Anti-motility agents should be avoided and proton pump inhibitor use should be reconsidered.
Development of Drug-Resistant Bacteria
Oral vancomycin use increases the chance of vancomycin-resistant *Enterococci* populations in the gastrointestinal tract. As a consequence, prudent use of oral vancomycin is advised
Cardiovascular and cerebrovascular effects
Cases of Kounis syndrome have been reported in patients treated with vancomycin. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

4.5 Interaction with other medicinal products and other forms of interaction

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, cisplatin and piperacillin/tazobactam may potentiate the nephrotoxicity and/or ototoxicity of vancomycin and consequently requires careful monitoring of the patient (see section 4.4).

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.

4.6 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, fetus or gestation period (see section 5.3).
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 clearly necessary. Vancomycin should be cautiously given to breast-feeding mothers because of potential adverse reactions in the infant (disturbances in the intestinal flora with diarrhea, colonization with yeast-like fungi and possibly sensibilization).
Considering the importance of this medicine for nursing mother, the decision to stop breastfeeding should be considered.

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

4.8 Undesirable effects
Summary of the Safety profile
The most common adverse reactions are phlebitis, pseudo-allergic reactions and flushing of the upper body (“red-neck syndrome”) in connection with too rapid intravenous infusion of vancomycin.

The absorption of vancomycin from the gastrointestinal tract is negligible. However, in severe inflammation of the intestinal mucosa, especially in

combination with renal insufficiency, adverse reactions that occur when vancomycin is administered parenterally may appear.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) have been reported in association with vancomycin treatment (see section 4.4).

Tabulated List of Adverse reactions

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The adverse reactions listed below are defined using the following 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)

System organ class	
Frequency	**Adverse reaction**
Blood and the lymphatic system disorders:	
Rare	Reversible neutropenia[1], agranulocytosis, eosinophilia, thrombocytopenia, pancytopenia.
Not known	Haemolytic anaemia
Immune system disorders:	
Rare	Hypersensitivity reactions, anaphylactic reactions[2]
Renal and urinary disorders:	
Common	Renal insufficiency manifested primarily by increased serum creatinine and serum urea
Rare	Interstitial nephritis, acute renal failure.
Not known	Acute tubular necrosis
General disorders and administration site conditions:	
Common	Phlebitis, redness of the upper body and face.
Rare	Drug fever, shivering, pain and muscle spasm of the chest and back muscles
Cardiac disorders	
Very rare	Cardiac arrest
Not known	Kounis syndrome
Vascular disorders:	
Common	Decrease in blood pressure
Rare	Vasculitis
Respiratory, thoracic and mediastinal disorders:	
Common	Dyspnoea, stridor
Gastrointestinal disorders:	
Rare	Nausea
Very rare	Pseudomembranous enterocolitis
Not known	Vomiting, diarrhoea
Hepatobiliary disorders:	
Common	Alanine aminotransferase increased, aspartate aminotransferase increased
Skin and subcutaneous tissue disorders:	
Common	Flushing of the upper body ("red man syndrome"), exanthema and mucosal inflammation, pruritus, urticaria
Very rare	Exfoliative dermatitis, Stevens-Johnson syndrome, Linear IgA bullous dermatosis[5] Toxic epidermal necrolysis (TEN)
Not known	Eosinophilia and systemic symptoms (DRESS syndrome), AGEP (Acute Generaliz Exanthematous Pustulosis)

Description of selected adverse drug reactions
Reversible neutropenia usually starting one week or more after onset of intravenous therapy or after total dose of more than 25 g.
During or shortly after rapid infusion anaphylactic/ anaphylactoid reactions including wheezing may occur. The reactions abate when administration is stopped, generally between 20 minutes and 2 hours. Vancomycin should be infused slowly (see sections 4.2 and 4.4). Necrosis may occur after intramuscular injection.
Tinnitus, possibly preceding onset of deafness, should be regarded as an indication to discontinue treatment.
Ototoxicity has primarily been reported in patients given high doses, or in those on concomitant treatment with other ototoxic medicinal products like aminoglycosides, or in those who had a pre-existing reduction in kidney function or hearing**.**
Pediatric population
The safety profile is generally consistent among children and adult patients. Nephrotoxicity has been described in children, usually in association with other nephrotoxic agents such as aminoglycosides.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via the relevant national regulatory authority pharmacovigilance.

4.9 Overdose

Toxicity due to overdose has been reported. 500 mg iv to a child, 2 years 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 hemodialysis or peritoneal dialysis. Hemofiltration or hemoperfusion with polysulfide resins have been used to reduce serum concentrations of vancomycin.

5. Pharmacological properties
5.1 Pharmacodynamic properties
Vancomycin is an amphoteric glycopeptide antimicrobial substance produced by the growth of certain strains of Nocardia orientalis. It is bactericidal against many gram-positive organisms.

5.2 Pharmacokinetic properties
Absorption
Vancomycin is administered intravenously for the treatment of systemic infections.
In the case of patients with normal renal function, intravenous infusion of multiple doses of 1g vancomycin (15 mg/kg) for 60 minutes produces

approximate average plasma concentrations of 50-60 mg/L, 20-25 mg/L and 5-10 mg/L, immediately, 2 hours and 11 hours after completing the infusion, respectively. The plasma levels obtained after multiple doses are similar to those achieved after a single dose.
Vancomycin is not usually absorbed into the blood after oral administration. However, absorption may occur after oral administration in patients with (pseudomembranous) colitis. This may lead to vancomycin accumulation in patients with co-existing renal impairment

Distribution

The volume of distribution is about 60 L/1.73 m^2 body surface. At serum concentrations of vancomycin of 10 mg/l to 100 mg/l, the binding of the drug to plasma proteins is approximately 30-55%, measured by ultra-filtration.
Vancomycin diffuses readily across the placenta and is distributed into cord blood. In non-inflamed meninges, vancomycin passes the blood-brain barrier only to a low extent.

Biotransformation

There is very little metabolism of the drug. After parenteral administration it is excreted almost completely as microbiologically active substance (approx. 75-90% within 24 hours) through glomerular filtration via the kidneys.

Elimination

The elimination half-life of vancomycin is 4 to 6 hours in patients with normal renal function and 2.2-3 hours in children. Plasma clearance is about 0.058 L/kg/h and kidney clearance about 0.048 L/kg/h. In the first 24 hours, approximately 80 % of an administered dose of vancomycin is excreted in the urine through glomerular filtration. Renal dysfunction delays the excretion of vancomycin. In anephric patients, the mean half-life is 7.5 days. Due to ototoxicity of vancomycin therapy-adjuvant monitoring of the plasma concentrations is indicated in such cases.
Biliary excretion is insignificant (less than 5% of a dose).
Although the vancomycin is not eliminated efficiently by hemodialysis or peritoneal dialysis, there have been reports of an increase in vancomycin clearance with hemoperfusion and hemofiltration.
After oral administration, only a fraction of the administered dose is recovered in the urine. In contrast, high concentrations of vancomycin are found in the feces (>3100 mg/kg with doses of 2 g/day)

Linearity/non-linearity

Vancomycin concentration generally increases proportionally with increasing dose. Plasma concentrations during multiple dose administration are similar to those after the administration of a single dose.

Characteristics in specific groups

Renal impairment

Vancomycin is primarily cleared by glomerular filtration. In patients with impaired renal function the terminal elimination half- life of vancomycin is prolonged and the total body clearance is reduced.

Subsequently, optimal dose should be calculated in line with dosing recommendations provided in section 4.2. Posology and method of administration.

Hepatic impairment

Vancomycin pharmacokinetics is not altered in patients with hepatic impairment.

Pregnant Women:

Significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant women (see Section 4.6).

Overweight patients

Vancomycin distribution may be altered in overweight patients due to increases in volume of distribution, in renal clearance and possible changes in plasma protein binding. In these subpopulations vancomycin serum concentration was found higher than expected in male healthy adults (see section 4.2).

In infants and older children, the volume of distribution ranges between 0.26-1.05 L/kg while clearance varies between 0.33-1.87 ml/kg/min.

Pediatric population

Vancomycin PK has shown wide inter-individual variability in preterm and term neonates. In neonates, after intravenous administration, vancomycin volume of distribution varies between 0.38 and 0.97 L/kg, similar to adult values, while clearance varies between 0.63 and 1.4 ml/kg/min. Half-life varies between 3.5 and 10 h and is longer than in adults, reflecting the usual lower values for clearance in the neonate.

5.3 Preclinical safety data

No reproduction tests were performed with the drug, so its effect on reproduction is not known. A conventional teratology study performed in female rats revealed no teratogenic effects and the same occurred in a similar study in female rabbits. In these species, the target organ of toxicity was the kidney.

Vancomycin has been studied in a number of standard studies *in vitro* and *in vivo* to determine the mutagenic potential, involving scanning of non-specific DNA damage, incidental mutations, chromosomal damage and loss of chromosomes.

The medicinal product was not genotoxic.

6. Pharmaceutical Particulars

6.1 List of Excipients

10ml sterile water for injection

6.2 Incompatibilities

None

6.3 Shelf-Life

24 months

6.4 Special Precautions for storage

Store below 30°C.

Protect from sunlight & moisture. Keep out of the reach of children.

6.5 Nature and Content of container

Each pack contains a glass vial containing 500mg of Vancomycin Hydrochloride with 10ml or 20ml of sterile water for injection as diluent.

6.6 Special precautions for disposal and other handling

Refer "4.2 Posology and method of administration

7. Marketing Authorization Holder

Nabiqasim Industries (Pvt.) Ltd. 17/24, Korangi Industrial Area, Korangi, Karachi – Pakistan.

8. Marketing Authorization Number

H2022/CTD6770/13308

9. Date of first authorization/renewal of the authorization

06/09/2022

10. Date of revision of the text

06/09/2022