SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vancosan 500 mg, Powder for solution for infusion
Vancosan 1000 mg, Powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains vancomycin hydrochloride corresponding to 500 mg or 1000 mg vancomycin, respectively.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for infusion.
Fine powder, white with pink to brown nuance.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe infections, caused by gram-positive bacteria susceptible to vancomycin which cannot be treated with or failed to respond or are resistant to other antibiotics such as penicillins and cephalosporins.

- endocarditis
- infections of the bones (osteitis, osteomyelitis) and joints
- infections of the lower respiratory tract (pneumonia / nosocomial pneumonia (NP) caused by bacteria)
- soft tissue infection

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

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.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

The dose should be individually adapted according to weight, age and renal function.

Patients with normal renal functions, adults and children from 12 years:
The usual intravenous dose is 500 mg every 6 hours or 1 g every 12 hours. In special circumstances and for severe and life threatening infections, 15-20 mg/kg body weight every 8-12 h might be considered to achieve optimal trough concentrations (see Monitoring of vancomycin serum concentrations in this section, and section 5.1).

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 (vancomycin plus rifampicin, gentamicin, streptomycin).
Enterococcal endocarditis is treated for 6 weeks with vancomycin in combination with an aminoglycoside. Official guidance should be consulted.

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.

Elderly patients:
The natural decrease of the glomerular filtration rate with higher age can result in an increased vancomycin serum concentration if dosage is not adapted (see table for dosage in case of impaired renal functions).

Paediatric population
Children (1 month to 12 years):
The usual intravenous daily dose is 40 mg/kg body weight, mostly in 4 single doses, that is 10 mg/kg body weight every 6 hours. The dose may be increased to 60 mg/kg bodyweight per day (see section 5.1).

Infants up to 1 month:
For young infants and new-borns the doses can be lower. The recommendation is an initial dose of 15 mg/kg body weight and maintenance doses of 10 mg/kg body weight every 12 hours in the first life week and then every 8 hours until the age of one month. The monitoring of serum levels may be necessary.

Patients with impaired renal functions
In patients with impaired renal function the dosage has to be adapted to the excretion rate. In that case the evaluation of the vancomycin serum level may be helpful, especially in severely ill patients with changing renal function.

The following dosage table can serve as guidance for patients with impaired renal function. The initial dose should be not less than 15 mg/kg body weight.

Creatinine clearance [ml/min]	Vancomycin dosage [mg/24 hours]
> 100	2000-1500
100-70	1500-1000
70-30	1000-500
20	300
10	150

Patients with anuria
The initial dose is 15 mg/kg to achieve therapeutic levels. The maintenance dose is about 1.9 mg/kg/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 with anuria, and also receiving a regular hemodialysis, the following dosage is possible: saturating dose 1000 mg, maintenance dose 1000 mg every 7-10 days.
If polysulfon membranes are used for hemodialysis („high flux dialysis“), the half time of vancomycin is shortened. For patients with regular hemodialysis a higher maintenance dose may be necessary.

Patients with hepatic impairment
There is no evidence that the dose has to be reduced in patients with hepatic insufficiency.

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. Depending on the site of infection and susceptibility of the pathogen, trough values of 15-20 mg/l may be needed to achieve efficacy (see sections 4.4 and 5.1).

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, as well single doses lower than 600 mg 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 whose fluid intake must be limited can also 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.

For information about the preparation of the solution, please see section 6.6.

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

4.3 Contraindications
Hypersensitivity to the active substance.

4.4 Special warnings and precautions for use

Warnings
In case of severe acute hypersensitivity reactions (e.g. anaphylaxis), the treatment with vancomycin has to be discontinued immediately and the usual appropriate emergency measures have to be started (e.g. antihistaminics, corticosteroides, and – if necessary – artificial respiration).

In case of acute anuria or of impairment of the cochlear apparatus vancomycin should only be used in vital indication.

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 g/l) 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.
Vancomycin must be administered only by intravenous use, owing to the risk of necrosis. The risk of venous irritation is minimised by giving vancomycin in the form of a dilute infusion and by changing the injection site.
The administration of vancomycin by intraperitoneal injection during continuous ambulatory peritoneal dialysis has been associated with a syndrome of chemical peritonitis.

Vancomycin should be used with care in patients with renal insufficiency as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations. 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. Additional care should be exercised if vancomycin is used concomitantly with other nephrotoxic drugs.

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. 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.
Vancomycin should be avoided in patients with previous hearing loss. If it is used in such patients, the dose should be regulated, by periodic determination of the drug level in the blood. The elderly are more susceptible to auditory damage.

Precautions
Vancomycin is very irritating to tissue and causes injection site necrosis if injected intramuscularly. Pain and thrombophlebitis may occur in many patients receiving vancomycin and are occasionally severe. The frequency and severity of thrombophlebitis can be minimised by administering the medicinal product slowly as a dilute solution (see section 6.6) and by changing the sites of infusion regularly. The frequency of infusion-related reactions (hypotension, flushing, erythema, urticaria and pruritus) increases with the concomitant administration of anaesthetic agents. This may be reduced by administering the vancomycin by infusion over 60 minutes, before anaesthetic induction.

Vancomycin should be used with caution in patients with allergic reactions to teicoplanin, since crossed hypersensitivity reactions between vancomycin and teicoplanin have been reported.

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.

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 haematologic studies, urine analysis, liver and renal function tests.

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.

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 section 4.2).

If vancomycin is administered over a longer period of time or together with medicinal products possibly leading to neutropenia, the blood picture has to be controlled regularly.

Paediatric use: Vancomycin should be used with particular care in premature infants and children, because of their renal immaturity and the possible increase in the serum concentration of vancomycin. The blood concentrations of vancomycin should therefore be monitored carefully. Concomitant administration of vancomycin and anaesthetic agents has been associated with erythema and histamine-like flushing in children (see section 4.5).

The frequency of infusion-related reactions (hypotension, flushing, erythema, urticaria and pruritus) increases with the concomitant administration of anaesthetic agents (see section 4.5).

In case of severe persistent diarrhoea the possibility of pseudomembranous enterocolitis that might be life-threatening has to be taken into account (see section 4.8). Anti-diarrhoeic medicinal products must not be given.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Other potentially nephro- or ototoxic medicinal products

A concomitant or sequential administration of vancomycin and other potentially oto- or nephrotoxic medicinal products can increase the oto- or nephrotoxicity. Particularly in cases of concomitant aminoglycoside administration, a careful monitoring is necessary. In these cases the maximum dose of vancomycin is to be limited to 500 mg every 8 hours.

Anaestetics

It is reported that the incidence of potential side effects (like hypotension, skin erubescence, erythema, urticaria and pruritus) increases when vancomycin is concomitantly administered with anesthetics. In order to avoid side effects, vancomycin should be administered at least 60 minutes before induction of the anaesthesia.

Muscle relaxants
If vancomycin hydrochloride is applied during or immediately after surgery, effects of concomitantly administered muscle relaxants (e. g. succinylcholin), such as neuromuscular block, can be intensified or prolonged.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Adequate data from the use of vancomycin during pregnancy are not available. Reproduction toxicological studies in animals do not suggest any effects on the gestation period or the development of the embryo and foetus (see section 5.3).
However, vancomycin crosses 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 breast milk and should therefore be used during the lactation period only if other antibiotics have failed. Caution should be used when vancomycin is 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 medical product for a nursing mother, a decision to stop breastfeeding should be considered.

4.7 Effects on ability to drive and use machines

Vancomycinhas no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The frequency of undesirable effects is rated corresponding to the following table:
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 side effects are phlebitis and pseudo-allergic reactions due to a rapid intravenous infusion of vancomycin.

Blood and lymphatic system disorders:
Rare: Agranulocytosis, neutropenia, thrombocytopenia, eosinophilia.

Immune system disorders:
Rare: Anaphylactoid reactions, hypersensitivity reactions.

Ear and labyrinth disorders:
Uncommon: Transient or persistent impairment of hearing functions.
Rare: Tinnitus, dizziness.

Cardiac disorders:
Very rare: Cardiac arrest.

Vascular disorders:

Common: Hypotension, thrombophlebitis.
Very rare: Vasculitis.

Respiratory, thoracic and mediastinal disorders:
Common: Dyspnoe, stridor.

Gastrointestinal disorders:
Rare: Nausea.
Very rare: Pseudomembranous enterocolitis.

Skin and subcutaneous tissue disorders:
Common: Exanthema and mucosal inflammation, pruritus, urticaria.
Rare: IgA-triggered bullous dermatosis.
Very rare: Severe skin reactions with life-threatening general symptoms (e. g. exfoliative dermatitis, Stevens-Johnson-syndrome or Lyell-syndrome), AGEP (Acute generalised exanthematous pustulosis).
Not known: DRESS (Drug Reactions with Eosinophilia and Systemic Symptoms).

Renal and urinary disorders:
Common: Renal insufficiency, manifested primarily by elevated serum creatinine or serum urea concentrations.
Rare: Interstitial nephritis and / or acute renal failure.
Not known: Acute tubular necrosis.

General disorders and administration site conditions
Common: Phlebitis, erubescence of the upper body („red neck“ or red man syndrome“), pain and spasms of the chest or back muscles.
Rare: Drug fever and chills.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*

4.9 Overdose
Toxicity due to overdose has been reported. 500 mg administered intravenously 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 haemodialysis or peritoneal dialysis. Haemofiltration or haemoperfusion with polysulfone resins have been used to reduce serum concentrations of vancomycin.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Glycopeptide antibacterials, ATC code: J01XA01

Mechanism of action:
Vancomycin is a tricyclic glycopeptide antibiotic that inhibits the syntesis of the cell wall in sensitive bacteria by binding with high affinity to the D-alanyl-D-alanine terminus of cell wall precursor units. The drug is bactericidal for dividing microorganisms.

PK/PD relationship:
Vancomycin displays concentration-independent activity with the area under the concentration curve (AUC) divided by the the minimum inhibitory concentration (MIC) of the target organism as the primary predictive parameter for efficacy. On basis of *in vitro*, animal and limited human data, an AUC/MIC ratio of 400 has been established as a PK/PD target to achieve clinical effectiveness with vancomycin. To achieve this target when MICs are > 0.5 mg/l, dosing in the upper range and high trough serum concentrations (15-20 mg/l) are required (see section 4.2).

Mechanism of resistance:
Acquired resistance to glycopeptides is based on acquisition of various van gene complexes and alteration of the D-alanyl-D-alanine target to D-alanyl-D-lactate or D-alanyl-D-serine which bind vancomycin poorly, because a critical site for hydrogen bonding is missing. This form of resistance is especially seen in *Enterococcus faecium*.
The reduced susceptibility or resistance to vancomycin in *Staphylococcus* is not well understood. Several genetic elements and multiple mutations are required.
Cross-resistance with teicoplanin has been reported.

Susceptibility:
Vancomycin is active against gram-positive bacteria. Gram-negative bacteria are resistant.

The MIC breakpoints separating susceptible from resistant organisms are as follows:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) recommendations

	Susceptible	Resistant
Staphylococcus spp.	≤ 2 mg/l	> 2 mg/l
Enterococcus spp.[1]	≤ 4 mg/l	> 4 mg/l
Streptococcus spp	≤ 2 mg/l	> 2 mg/l
Streptococcus pneumoniae	≤ 2 mg/l	> 2 mg/l
Gram-positive anaerobes	≤ 2 mg/l	> 2 mg/l
Non species related[2]	≤ 2 mg/l	> 4 mg/l

[1] The S/I breakpoint for vancomycin has been raised to 4 mg/l to avoid dividing the wild type MIC distributions of some species.

[2] Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

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 in at least some types of infections is questionable.

Commonly susceptible species

Gram positive *Enterococcus faecalis*. *Staphylococcus aureus* *Staphylococcus* coagulase negative *Streptococcus* spp. *Streptococcus pneumoniae* *Clostridium* spp.
Species for which acquired resistance may be a problem *Enterococcus faecium*
Inherently resistant Gram negative bacteria *Chlamydia* spp. Mycobacteria *Mycoplasma* spp. *Rickettsia* spp.

5.2 Pharmacokinetic properties

Absorption

The mean plasma levels after intravenous infusion of 1 g vancomycin over 60 minutes were approximately 63 mg/l at the end of infusion, approximately 23 mg/l after 2 hours , and approximately 8 mg/l after 11 hours.

If vancomycin is administered during a peritonealdialysis intraperitoneally, approximately 60% reach the systemic cycle during the first 6 hours. After intraperitoneal administration of 30 mg/kg serum levels of approximately 10 mg/l are reached.

Distribution

After intravenous administration vancomycin is distributed in nearly all tissues. In pleura, pericard, ascites and synovia liquid as well as in heart muscle and in heart valve concentrations similar to those in blood plasma are achieved. The apparent distribution volume in the steady state is named to be 0.43 (up to 0.9) l/kg. In case of non-inflammatory meninges only small quantities of vancomycin pass into the cerebrospinal fluid.

Elimination

Vancomycin is bound to plasma proteins to 55%. It is metabolised only to a small extent. After parenteral administration it is excreted renally via glomerular filtration, nearly completely as the microbiologcally active substance (approximately 70-80% within 24 h). Biliar excretion has low relevance (less than 5% of a dose).

The serum half life in adult patients with normal renal functions is about 4-6 hours, in children 2.2-3 hours. Impaired renal function can prolong the elimination (up to 7.5 days).

The clearance of vancomycin from the plasma correlates approximately with the glomerular filtration rate. The total systemic and renal clearance of vancomycin can be reduced in elderly patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

Limited data on mutagenic effects are available, they show no indication of any hazard. Long-term studies in animals regarding a carcinogenic potential are not available. In teratogenicity studies, where rats and rabbits received doses approximately corresponding to the human dose based on body surface (mg/m^2), no direct or indirect teratogenic effects were observed.

Animal studies of the use during the perinatal/postnatal period and regarding effects on fertility are not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Vancomycin solutions have a low pH value, which can lead to chemical or physical instability if mixed with other substances. Therefore, each parenteral solution should be checked visually for precipitations or discolouration prior to use. To avoid precipitation, syringes and intravenous catheters should be rinsed with physiological sodium chloride solution between the administration of Vancosan and other medicines.

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

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.

6.3 Shelf life

2 years

Shelf-life of the prepared solution for infusion

Chemical and physical in-use stability of the prepared solution for infusion has been demonstrated for 96 hours at 2-8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, the total in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless type I glass vials with bromobutyl rubber stopper and flip-off cap.
Packages with 1, 5 or 10 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The powder must be reconstituted and the resulting concentrate must then be diluted further prior to use.

Preparation of the infusion concentrate

Dissolve the contents of a 500 mg vancomycin vial in 10 ml of sterile water for injections.
Dissolve the contents of a 1000 mg vancomycin vial in 20 ml of sterile water for injections.
One ml of reconstituted solution contains 50 mg of vancomycin.

Preparation of the solution for infusion
The infusion concentrate may be diluted with sterile water for injections, 9 mg/ml sodium chloride or 50 mg/ml glucose.
Vial containing 500 mg vancomycin: To obtain a 5 mg/ml solution for infusion dilute 10 ml of the infusion concentrate with 90 ml of the diluent.
Vial containing 1000 mg vancomycin: To obtain a 5 mg/ml solution for infusion dilute 20 ml of the infusion concentrate with 180 ml of the diluent.
The concentration of vancomycin in the solution for infusion must not exceed 2.5-5 mg/ml.

Appearance of solution for infusion
The solution is to be inspected visually for particulate matter and discolouration prior to administration. The solution must only be used if the solution is clear and free from particles.
For storage conditions of the diluted medicinal product, see sections 6.3.

Administration
The desired dose should be administered slowly by intravenous infusion at a rate of no more than 10 mg/minute, for at least 60 minutes or even longer.
To prevent precipitation due to the low pH of vancomycin hydrochloride in solution, all intravenous cannulae and catheters should be flushed with saline.

Vancomycin solutions are basically administered separately, if the chemical and physical compatibility with another infusion solution is not proven (see section 6.2).

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

7. MARKETING AUTHORISATION HOLDER
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8. MARKETING AUTHORISATION NUMBER(S)
(to be completed/adapted nationally)

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2011-03-10

10. DATE OF REVISION OF THE TEXT
2014-11-13