Public Assessment Report

Decentralised Procedure

Vancomycin 500mg Powder for Solution for Infusion
Vancomycin hydrochloride 500mg Powder for Solution for Infusion
Vancomycin 1000mg Powder for Solution for Infusion
Vancomycin hydrochloride 1000mg Powder for Solution for Infusion

UK/H/1383-4/001-2/DC
UK licence no: PL 18585/0016-7, 0019-20

Billev Pharma APS
Vancomycin 500mg Powder for Solution for Infusion

Vancomycin hydrochloride 500mg Powder for Solution for Infusion

Vancomycin 1000mg Powder for Solution for Infusion

Vancomycin hydrochloride 1000mg Powder for Solution for Infusion

LAY SUMMARY

On 9th November 2009, the UK granted Billev Pharma APS Marketing Authorisation (licences) for the medicinal products Vancomycin 500mg and 1000mg powder for solution for infusion and Vancomycin hydrochloride 500mg and 1000mg powder for solution for infusion. These prescription-only medicines are indicated in the therapy of severe, potentially life-threatening infections due to susceptible gram-positive microorganisms which cannot be treated with or have failed to respond to other effective, less toxic antimicrobial medicinal products, such as penicillins and cephalosporins.

Vancomycin belongs to a group of glycopeptides antibiotics which eliminate bacteria that cause many kinds of infections, including pneumonia and skin, bone and heart valve infections.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Vancomycin powder for Solution for Infusion outweigh the risks and Marketing Authorisations were granted.
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## Module 1

| **Product Name** | Vancomycin 500mg and 1000mg Powder for Solution for Infusion  
Vancomycin hydrochloride 500mg and 1000mg Powder for Solution for Infusion |
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| **MA Holder** | Billev Pharma APS  
Fuglebaekgaard Elmegardsvej 1A, DK-3630 Jaegerspris  
Denmark |
| **RMS** | UK |
| **CMS** | LV, IT, FI, ES, NL, EE, DK, CZ, BG, BE, SK, SI, SE, PT, DE, LU and PL |
| **Procedure Number** | UK/H/1383-4/01-2/DC |
| **Timetable** | Day 210 – 15th October 2009 |
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Vancomycin, 500 mg, powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 500 mg vancomycin (hydrochloride) equivalent to 500,000 IU.

3 PHARMACEUTICAL FORM
Powder for solution for infusion.
White or almost white powder.

After reconstitution a solution is obtained with a pH of approximately 3.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Vancomycin solution, used intravenously is indicated in the therapy of severe, potentially life-threatening infections due to susceptible gram-positive microorganisms which cannot be treated with or failed to respond to other effective, less toxic antimicrobial medicinal products, such as penicillins and cephalosporins.

Vancomycin should be reserved for those cases where there is a specific indication, to minimize the chance of resistance emerging.

Vancomycin is useful in the treatment of the following severe infections caused by susceptible microorganisms (see section 5.1):
- endocarditis,
- infections of bones (osteomyelitis),
- pneumonia,
- soft-tissue infections.

Endocarditis caused by enterococci, *Streptococcus viridans* or *S. bovis* should be treated with a combination of vancomycin and an aminoglycoside.

Vancomycin may be used in certain patients who cannot tolerate penicillins and other beta-lactam antibiotics, in the antibiotic prophylaxis in case of high risk for bacterial endocarditis or perioperatively for major surgical procedures (e.g., cardiac and vascular procedures, etc).

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

4.2 Posology and method of administration
*Vancomycin powder for solution for infusion must be administered intravenously. Each dose should be administered at a rate not exceeding 10 mg/min or over a period of time of at least 60 minutes (whichever is longer).*

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

The following dosage regimens are recommended:

Patients with normal renal function

*Adults and adolescents above 12 years of age:*
*The recommended daily intravenous dose is 2000mg, divided into doses of 500mg every 6 hours or 1000mg every 12 hours.*

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 (gentamicin plus rifampin, gentamicin, streptomycin).

Enterococcal endocarditis is treated for 6 weeks with vancomycin in combination with an aminoglycoside – according to national recommendations.

Peri-operative prophylaxis: 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.
Children one month to 12 years of age:
The recommended intravenous dose is 10mg/kg, every 6 hours or 20 mg/kg every 12 hours.

Infants and newborns:
The recommended initial dose is 15 mg/kg, followed by 10 mg/kg every 12 hours during the first week of life and every 8 hours after that age and up to 1 month of age. Careful monitoring of serum concentration of vancomycin is recommended (see below).

Elderly patients:
Lower maintenance doses may be required due to the age-related reduction in renal function.

Obese patients:
Modification of the usual daily doses may be required.

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

Patients with impaired renal function
The dose must be adjusted in patients with impaired renal function and the following nomogram can serve as guidance. Careful monitoring of serum concentration of vancomycin is recommended (see below).

Dosing nomogram for adults with impaired renal function

In patients with mild or moderate renal failure, the starting dose must not be less than 15 mg/kg. In patients with severe renal failure, it is preferable to administer a maintenance dose between 250 mg and 1000 mg at a spacing of several days rather than administer lower daily doses.

Patients with anuria (with practically no renal function) should receive a dose of 15 mg/kg body weight until the therapeutic serum concentration is reached. The maintenance doses are 1.9 mg/kg body weight per 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 without any renal function, even under regular hemodialysis, the following dosage is also possible: Saturating dose 1000 mg, maintenance dose 1000 mg every 7 - 10 days.

If polysulfone membranes are used in haemodialysis (high flux dialysis), the half-life of vancomycin is reduced. An additional maintenance dose may be necessary in patients on regular haemodialysis.

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. 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 – 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 requiring fluid restriction can 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 refer to chapter 6.6.

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

4.3 Contraindications
Hypersensitivity to vancomycin

4.4 Special warnings and precautions for use

Warnings:
In the presence of acute anuria or cochlear damage, vancomycin must be used only when absolutely necessary and if no other safer alternatives are available.

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, corticosteroids, and – if necessary – artificial respiration).

Rapid bolus administration (i.e. over several minutes) may be associated with severe hypotension (including shock and rare 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 minimized 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.

Nephrotoxicity: vancomycin must be used with caution in patients with renal failure as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations. In the treatment of these patients and in those who are receiving concomitant treatment with other nephrotoxic active substances (i.e. aminoglycosides), serial tests of renal function must be performed and the appropriate dose regimens adhered to in order to reduce the risk of nephrotoxicity to a minimum (see section 4.2).

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. 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.

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 minimized 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.

Prolonged use of vancomycin may lead to superinfections with resistant microorganisms, therefore such patients should be regulatory monitored. If superinfection occurs during therapy, appropriate measures should be taken. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including vancomycin, and may range in the severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of vancomycin. Antiperistaltics are contraindicated.

Regular monitoring of the blood levels of vancomycin is indicated in 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.

Doses should be titrated on the basis of serum levels. Blood levels should be monitored and renal function tests performed regularly.

It is a general recommendation to monitor the concentrations 2-3 times weekly.

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.

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. The concomitant use of vancomycin and anaesthetic agents in children has been associated with erythema and anaphylactoid reactions. If the administration of vancomycin is required for surgical prophylaxis, it is advisable to administer the anaesthetic agents after completion of the vancomycin infusion.

### 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/nephrotoxic active substances particularly gentamycin, amphotericin B, streptomycin, neomycin, kanamycin, amikacin, tobramycin, viomycin, bacitracin, polymyxin B, colistin and cisplatin may potentiate the nephrotoxicity and/or ototoxicity of vancomycin and consequently requires careful monitoring of the patient.

Because of synergic action (e.g. with gentamycin) in these cases the maximum dose of vancomycin has to be restricted to 500 mg every 8 hours.

**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, foetus 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 other antibiotics have failed. Vancomycin should be cautiously 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 sensitisation). Considering the importance of this medicine for nursing mother, the decision should 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**
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The adverse reactions listed below is 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).

The most common adverse reactions are phlebitis and pseudo-allergic reactions in connection with too rapid intravenous use of vancomycin.

**Blood and the lymphatic system disorders**

*Rare* (≥ 10,000 to ≤ 1/1,000): thrombocytopenia, neutropenia, agranulocytosis, eosinophilia.

**Immune system disorders**

*Rare* (≥ 10,000 to ≤ 1/1,000): anaphylactic reactions, hypersensitivity reactions.

**Ear and labyrinth disorders**

*Uncommon* (≥ 1,000 to ≤ 1/100): transient or permanent loss of hearing.

*Rare* (≥ 10,000 to ≤ 1/1,000): tinnitus, dizziness.

**Cardiac disorders**

*Very rare* (≤ 1/10,000): cardiac arrest.

**Vascular disorders**

*Common* (>1/100 to ≤ 1/10): decrease in blood pressure, thrombophlebitis.

*Rare* (≥ 10,000 to ≤ 1/1,000): vasculitis.

**Respiratory, thoracic and mediastinal disorders**

*Common* (>1/100 to ≤ 1/10): dyspnoea, stridor.

**Gastrointestinal disorders**

*Rare* (≥ 10,000 to ≤ 1/1,000): nausea.

*Very rare* (≤ 1/10,000): pseudomembranous enterocolitis.

**Skin and subcutaneous tissue disorders**

*Common* (>1/100 to ≤ 1/10): exanthema and mucosal inflammation, pruritus, urticaria.

*Very rare* (≤ 1/10, 000): exfoliative dermatitis, Stevens-Johnson syndrome, Lyell’s syndrome, IgA induced bullous dermatitis.

**Renal and urinary disorders**

*Common* (>1/100 to ≤ 1/10): renal insufficiency manifested primarily by increased serum creatinine or serum urea concentrations.

*Rare* (≥ 10,000 to ≤ 1/1,000): interstitial nephritis, acute renal failure.

**General disorders and administration site conditions**

*Common* (>1/100 to ≤ 1/10): redness of the upper body and the face, pain and spasm of the chest and back muscles.

*Rare* (≥ 10,000 to ≤ 1/1,000): drug fever, shivering.

During or shortly after rapid infusion anaphylactic reactions may occur. The reactions abate when administration is stopped, generally between 20 minutes and 2 hours after having stopped administration.

Ototoxicity has primarily been reported in patients given high doses, or concomitant treatment with other ototoxic medicinal products, or with pre-existing reduction in kidney function or hearing.”
4.9 Overdose
Toxicity due to overdose has been reported. 500 mg IV to a child, 2 year 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
General properties
ATC classification
Pharmacotherapeutic group: glycopeptide antibacterials, ATC code: J01XA01.

Mode of action
Vancomycin is a glycopeptide antibiotic. Vancomycin has a bactericidal effect on proliferating germs by inhibiting the biosynthesis of the cell wall. In addition, it impairs the permeability of the bacterial cell membrane and RNA synthesis.

Mechanism(s) of resistance
Acquired resistance to glycopeptides is based on acquisition of various van gene complexes. Van genes have rarely been found in Staphylococcus aureus, where changes in cell wall structure result in “intermediate” susceptibility, which is most commonly heterogeneous.
There is no cross-resistance between vancomycin and other antibiotics but cross-resistance with other glycopeptide antibiotics, such as teicoplanin, does occur. Secondary development of resistance during therapy is rare.
In some countries, increasing cases of resistance are observed particularly in enterococci; multi-resistant strains of Enterococcus faecium are especially alarming.

Synergism
The combination of vancomycin with an aminoglycoside antibiotic has a synergistic effect against many strains of Staphylococcus aureus, non-enterococcal D-streptococci, enterococci and streptococci of the Viridans group. The combination of vancomycin with a cephalosporin has a synergistic effect against some oxacillin-resistant Staphylococcus epidermidis strains, and the combination of vancomycin with rifampicin has a synergistic effect against Staphylococcus epidermidis and a partial synergistic effect against some Staphylococcus aureus strains. As vancomycin in combination with a cephalosporin may also have an antagonistic effect against some Staphylococcus epidermidis strains and in combination with rifampicin against some Staphylococcus aureus strains, preceding synergism testing is useful.
Specimens for bacterial cultures should be obtained in order to isolate and indentify the causative organisms and to determine their susceptibility to vancomycin.

Breakpoints
Minimum inhibitory concentration (MIC) breakpoint established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Staphylococcus spp. and Streptococcus spp are Susceptible ≤ 2 mg/L and Resistant > 2 mg/L; for Enterococcus spp. are Susceptible ≤ 4 mg/L and Resistant > 4 mg/L; and for non-species related are Susceptible ≤ 2 mg/L and Resistant > 4 mg/L.

Susceptibility
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 is at least some types of infections is questionable.

Vancomycin has a narrow spectrum of action.

<table>
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<th>Commonly susceptible species</th>
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<tr>
<td>Staphylococcus spp</td>
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5.2 Pharmacokinetic properties

- **Distribution:** Following intravenous administration, vancomycin is distributed to almost all tissues and diffuses in pleural, pericardial, ascitic and synovial fluid as well as in the cardiac muscle and in heart valves. Comparable high concentrations are achieved as in blood plasma. Data about the vancomycin concentrations in bone (spongiosa, compacta) vary widely. The apparent distribution volume in steady state is stated to be 0.43 (up to 0.9) L/kg. In non-inflamed meninges vancomycin passes the blood-brain barrier only to a low extent. Vancomycin is bound to plasma proteins at 30 to 55 % and even higher.

- **Elimination:** Vancomycin is metabolized only to a low extent. After parenteral administration it is excreted almost completely as microbiologically active substance (approx. 75-90% within 24 hours) through glomerular filtration via the kidneys. Biliary excretion is insignificant (less than 5% of a dose).

In patients with normal renal function the half-life in serum is about 4-6 (5-11) hours, in children 2.2-3 hours. In impaired renal function, the half-life of vancomycin may be considerably prolonged (up to 7.5 days). Due to ototoxicity of vancomycin therapy-adjuvant monitoring of the plasma concentrations is indicated in such cases.

Mean plasma concentrations after i.v. infusion of 1000 mg vancomycin over 60 minutes were about 63 mg/L at the end of the infusion, about 23 mg/L after 2 hours and about 8 mg/L after 11 hours.

The clearance of vancomycin from plasma correlates nearly with the glomerular filtration rate.

The total systemic and renal clearance of vancomycin can be reduced in elderly patients.

As studies in anephric patients showed, the metabolic clearance seems to be very low. No vancomycin metabolites have been identified so far in humans.

If vancomycin is given during a peritoneal dialysis via the intraperitoneal route, approx. 60% reaches the systemic circulation during 6 hours. After i.p. administration of 30 mg/kg BW, serum levels of approx. 10 mg/l are achieved.

In case of oral use, high-polar vancomycin is virtually not absorbed. It appears after oral administration in active form in the stool, and is therefore a suitable chemotherapeutic for pseudomembranous colitis and staphylococcal colitis.

Vancomycin diffuses readily across the placenta and is distributed into cord blood.

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 show negative results, 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/m²), 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. This may lead to chemical or physical instability if mixed with other substances. Therefore, each parenteral solution should be checked visually for precipitations and discolouration prior to use.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
**Combination therapy**
In case of combination therapy of vancomycin with other antibiotics/chemotherapeutics, the preparations should be administered separately.

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

**Powder:**
3 years

Reconstituted solution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and 96 hours at 2-8°C.

Further diluted solution:
Solutions for infusion that are diluted to 5 mg/ml with 5% Glucose Injection or 0.9% Sodium Chloride Injection are chemically and physically stable in a refrigerator (2°C - 8°C) for 48 hours, or at 25°C for 24 hours.

Solutions for infusion that are diluted to 5 mg/ml with 5% Glucose Injection + 0.9% Sodium Chloride Injection are chemically and physically stable in refrigerator (2°C - 8°C) for 48 hours, or at 25°C for 24 hours.

From a microbiological point of view the medicinal product should be used immediately unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

### 6.4 Special precautions for storage

**Powder:**
Store below 25°C.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

### 6.5 Nature and contents of container

Colourless type I 15 ml glass vial, with a bromobutyl rubber stopper and an aluminium/plastic flip-off cap.

Pack sizes: 1, 5, 10 and 100 vials.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

**Preparation of the reconstituted solution**
Dissolve Vancomycin 500 mg Powder for solution for infusion in 10 ml of sterile Water for injection

One ml of reconstituted solution contains 50 mg of vancomycin.

**Appearance of reconstituted solution**
After reconstitution the solution is clear and colorless to slightly yellowish brown without visible particles.

For storage conditions of the reconstituted medicinal product, see section 6.3.

**Preparation of final diluted Solution for infusion**
Reconstituted solutions containing 50 mg/ml of vancomycin should be further diluted.

*Suitable diluents are:*
- 5% Glucose Injection
- 0.9% Sodium Chloride Injection
- 5% Glucose Injection with 0.9% Sodium Chloride Injection.

**Intermittent infusion:**
Reconstituted solution containing 500 mg of vancomycin (50 mg/ml) must be diluted further with at least 100 ml diluent (to 5mg/ml).

The concentration of vancomycin in Solution for infusion should not exceed 5 mg/ml. The desired dose should be administered slowly by intravenous use at a rate of no more than 10 mg/minute, for at least 60 minutes or even longer.

Continuous infusion:
This should be used only if treatment with an intermittent infusion is not possible. Dilute 1000 mg to 2000 mg of dissolved vancomycin in a sufficient amount of the above suitable diluent and administer it in the form of a drip infusion, so that the patient will receive the prescribed daily dose in 24 hours.

Appearance of diluted solution
After dilution the solution is clear and colorless without visible particles.

For storage conditions of the diluted medicinal product, see section 6.3.

Before administration, the reconstituted and diluted solutions should be inspected visually for particulate matter and discoloration. Only clear, and colorless solution free from particles should be used.

Disposal
Vials are for single use only. Unused medicinal products must be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
1 **NAME OF THE MEDICINAL PRODUCT**
Vancomycin hydrochloride 500 mg, powder for solution for infusion

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each vial contains 500 mg vancomycin (hydrochloride) equivalent to 500,000 IU.

3 **PHARMACEUTICAL FORM**
Powder for solution for infusion.
White or almost white powder.

After reconstitution a solution is obtained with a pH of approximately 3.

4 **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**
Vancomycin solution, used intravenously is indicated in the therapy of severe, potentially life-threatening infections due to susceptible gram-positive microorganisms which cannot be treated with or failed to respond to other effective, less toxic antimicrobial medicinal products, such as penicillins and cephalosporins.

Vancomycin should be reserved for those cases where there is a specific indication, to minimize the chance of resistance emerging.

Vancomycin is useful in the treatment of the following severe infections caused by susceptible microorganisms (see section 5.1):
- endocarditis,
- infections of bones (osteomyelitis),
- pneumonia,
- soft-tissue infections.

Endocarditis caused by enterococci, *Streptococcus viridans* or *S. bovis* should be treated with a combination of vancomycin and an aminoglycoside.

Vancomycin may be used in certain patients who cannot tolerate penicillins and other beta-lactam antibiotics, in the antibiotic prophylaxis in case of high risk for bacterial endocarditis or perioperatively for major surgical procedures (e.g., cardiac and vascular procedures, etc).

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

4.2 **Posology and method of administration**
*Vancomycin powder for solution for infusion must be administered intravenously. Each dose should be administered at a rate not exceeding 10 mg/min or over a period of time of at least 60 minutes (whichever is longer). The dose should be individually adapted according to weight, age and renal function.*

The following dosage regimens are recommended:

- **Patients with normal renal function**

  *Adults and adolescents above 12 years of age:*
  The recommended daily intravenous dose is 2000 mg, divided into doses of 500 mg every 6 hours or 1000 mg every 12 hours.

  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 (gentamicin plus rifampin, gentamicin, streptomycin).
  Enterococcal endocarditis is treated for 6 weeks with vancomycin in combination with an aminoglycoside – according to national recommendations.

  Peri-operative prophylaxis: 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.

  *Children one month to 12 years of age:*
  The recommended intravenous dose is 10 mg/kg, every 6 hours or 20 mg/kg every 12 hours.

  *Infants and newborns:*
The recommended initial dose is 15 mg/kg, followed by 10 mg/kg every 12 hours during the first week of life and every 8 hours after that age and up to 1 month of age. Careful monitoring of serum concentration of vancomycin is recommended (see below).

**Elderly patients:**
Lower maintenance doses may be required due to the age-related reduction in renal function.

**Obese patients:**
Modification of the usual daily doses may be required.

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

**Patients with impaired renal function**
The dose must be adjusted in patients with impaired renal function and the following nomogram can serve as guidance. Careful monitoring of serum concentration of vancomycin is recommended (see below).

![Dosing nomogram for adults with impaired renal function](image)

In patients with mild or moderate renal failure, the starting dose must not be less than 15 mg/kg. In patients with severe renal failure, it is preferable to administer a maintenance dose between 250 mg and 1000 mg at a spacing of several days rather than administer lower daily doses.

Patients with *anuria* (with practically no renal function) should receive a dose of 15 mg/kg body weight until the therapeutic serum concentration is reached. The maintenance doses are 1.9 mg/kg body weight per 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 without any renal function, even under regular hemodialysis, the following dosage is also possible:
Saturating dose 1000 mg, maintenance dose 1000 mg every 7 - 10 days.

If polysulfone membranes are used in haemodialysis (high flux dialysis), the half-life of vancomycin is reduced. An additional maintenance dose may be necessary in patients on regular haemodialysis.

**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.

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 – 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 requiring fluid restriction can 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 refer to chapter 6.6.

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

4.3 Contraindications
Hypersensitivity to vancomycin

4.4 Special warnings and precautions for use

Warnings:
In the presence of acute anuria or cochlear damage, vancomycin must be used only when absolutely necessary and if no other safer alternatives are available.

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, corticosteroids, and – if necessary – artificial respiration).

Rapid bolus administration (i.e. over several minutes) may be associated with severe hypotension (including shock and rare 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 minimized 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.

Nephrotoxicity: vancomycin must be used with caution in patients with renal failure as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations. In the treatment of these patients and in those who are receiving concomitant treatment with other nephrotoxic active substances (i.e. aminoglycosides), serial tests of renal function must be performed and the appropriate dose regimens adhered to in order to reduce the risk of nephrotoxicity to a minimum (see section 4.2).

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. 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.

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 minimized 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.

Prolonged use of vancomycin may lead to superinfections with resistant microorganisms, therefore such patients should be regularly monitored. If superinfection occurs during therapy, appropriate measures should be taken. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including vancomycin, and may range in the severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of vancomycin. Antiperistaltics are contraindicated.

Regular monitoring of the blood levels of vancomycin is indicated in 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.

Doses should be titrated on the basis of serum levels. Blood levels should be monitored and renal function tests performed regularly.

It is a general recommendation to monitor the concentrations 2-3 times weekly. 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.

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. The concomitant use of vancomycin and anaesthetic agents in children has been associated with erythema and anaphylactoid reactions. If the administration of vancomycin is required for surgical prophylaxis, it is advisable to administer the anaesthetic agents after completion of the vancomycin infusion.

### 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 and cisplatin may potentiate the nephrotoxicity and/or ototoxicity of vancomycin and consequently requires careful monitoring of the patient. Because of synergic action (e.g. with gentamycin) in these cases the maximum dose of vancomycin has to be restricted to 500 mg every 8 hours.

**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, foetus 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 other antibiotics have failed. Vancomycin should be cautiously 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 sensitisation).
Considering the importance of this medicine for nursing mother, the decision should 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**
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The adverse reactions listed below is 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).

The most common adverse reactions are phlebitis and pseudo-allergic reactions in connection with too rapid intravenous use of vancomycin.

Blood and the lymphatic system disorders
*Rare (≥ 10,000 to ≤ 1/1,000):* thrombocytopenia, neutropenia, agranulocytosis, eosinophilia.

Immune system disorders
*Rare (≥ 10,000 to ≤ 1/1,000):* anaphylactic reactions, hypersensitivity reactions.

Ear and labyrinth disorders
*Uncommon (≥ 1,000 to ≤ 1/100):* transient or permanent loss of hearing.
*Rare (≥ 10,000 to ≤ 1/1,000):* tinnitus, dizziness.

Cardiac disorders
*Very rare (≤ 1/10,000):* cardiac arrest.

Vascular disorders
*Common (>1/100 to ≤ 1/10):* decrease in blood pressure, thrombophlebitis.
*Rare (≥ 10,000 to ≤ 1/1,000):* vasculitis.

Respiratory, thoracic and medistinal disorders
*Common (>1/100 to ≤ 1/10):* dyspnoea, stridor.

Gastrointestinal disorders
*Rare (≥ 10,000 to ≤ 1/1,000):* nausea.
*Very rare (≤ 1/10,000):* pseudomembranous enterocolitis.

Skin and subcutaneous tissue disorders
*Common (>1/100 to ≤ 1/10):* exanthema and mucosal inflammation, pruritus, urticaria.
*Very rare (≤ 1/10, 000):* exfoliative dermatitis, Stevens-Johnson syndrome, Lyell’s syndrome, IgA induced bullous dermatitis.

Renal and urinary disorders
*Common (>1/100 to ≤ 1/10):* renal insufficiency manifested primarily by increased serum creatinine or serum urea concentrations.
*Rare (≥ 10,000 to ≤ 1/1,000):* interstitial nephritis, acute renal failure.

General disorders and administration site conditions
*Common (>1/100 to ≤ 1/10):* redness of the upper body and the face, pain and spasm of the chest and back muscles.
*Rare (≥ 10,000 to ≤ 1/1,000):* drug fever, shivering.

During or shortly after rapid infusion anaphylactic reactions may occur. The reactions abate when administration is stopped, generally between 20 minutes and 2 hours after having stopped administration.

Ototoxicity has primarily been reported in patients given high doses, or concomitant treatment with other ototoxic medicinal products, or with pre-existing reduction in kidney function or hearing.”
4.9 Overdose
Toxicity due to overdose has been reported. 500 mg IV to a child, 2 year 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

General properties

ATC classification
Pharmacotherapeutic group: glycopeptide antibacterials, ATC code: J01XA01.

Mode of action
Vancomycin is a glycopeptide antibiotic. Vancomycin has a bactericidal effect on proliferating germs by inhibiting the biosynthesis of the cell wall. In addition, it impairs the permeability of the bacterial cell membrane and RNA synthesis.

Mechanism(s) of resistance
Acquired resistance to glycopeptides is based on acquisition of various van gene complexes. Van genes have rarely been found in Staphylococcus aureus, where changes in cell wall structure result in “intermediate” susceptibility, which is most commonly heterogeneous.
There is no cross-resistance between vancomycin and other antibiotics but cross-resistance with other glycopeptide antibiotics, such as teicoplanin, does occur. Secondary development of resistance during therapy is rare.
In some countries, increasing cases of resistance are observed particularly in enterococci; multi-resistant strains of Enterococcus faecium are especially alarming.

Synergism
The combination of vancomycin with an aminoglycoside antibiotic has a synergistic effect against many strains of Staphylococcus aureus, non-enterococcal Dstreptococci, enterococci and streptococci of the Viridans group. The combination of vancomycin with a cephalosporin has a synergistic effect against some oxacillin-resistant Staphylococcus epidermidis strains, and the combination of vancomycin with rifampicin has a synergistic effect against Staphylococcus epidermidis and a partial synergistic effect against some Staphylococcus aureus strains. As vancomycin in combination with a cephalosporin may also have an antagonistic effect against some Staphylococcus epidermidis strains and in combination with rifampicin against some Staphylococcus aureus strains, preceding synergism testing is useful. Specimens for bacterial cultures should be obtained in order to isolate and indentify the causative organisms and to determine their susceptibility to vancomycin.

Breakpoints

Minimum inhibitory concentration (MIC) breakpoint established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Staphylococcus spp. and Streptococcus spp. are Susceptible ≤ 2 mg/L and Resistant > 2 mg/L; for Enterococcus spp. are Susceptible ≤ 4 mg/L and Resistant > 4 mg/L; and for non-species related are Susceptible ≤ 2 mg/L and Resistant > 4 mg/L.

Susceptibility
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 is at least some types of infections is questionable.

Vancomycin has a narrow spectrum of action.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus spp</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
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</tbody>
</table>
5.2 Pharmacokinetic properties

- **Distribution:** Following intravenous administration, vancomycin is distributed to almost all tissues and diffuses in pleural, pericardial, ascitic and synovial fluid as well as in the cardiac muscle and in heart valves. Comparable high concentrations are achieved as in blood plasma. Data about the vancomycin concentrations in bone (spongiosa, compacta) vary widely. The apparent distribution volume in steady state is stated to be 0.43 (up to 0.9) L/kg. In non-inflamed meninges vancomycin passes the blood-brain barrier only to a low extent. Vancomycin is bound to plasma proteins at 30 to 55% and even higher.

- **Elimination:** Vancomycin is metabolized only to a low extent. After parenteral administration it is excreted almost completely as microbiologically active substance (approx. 75-90% within 24 hours) through glomerular filtration via the kidneys. Biliary excretion is insignificant (less than 5% of a dose).

In patients with normal renal function the half-life in serum is about 4-6 (5-11) hours, in children 2.2-3 hours. In impaired renal function, the half-life of vancomycin may be considerably prolonged (up to 7.5 days). Due to ototoxicity of vancomycin therapy-adjuvant monitoring of the plasma concentrations is indicated in such cases.

Mean plasma concentrations after i.v. infusion of 1000 mg vancomycin over 60 minutes were about 63 mg/L at the end of the infusion, about 23 mg/L after 2 hours and about 8 mg/L after 11 hours.

The clearance of vancomycin from plasma correlates nearly with the glomerular filtration rate.

The total systemic and renal clearance of vancomycin can be reduced in elderly patients.

As studies in anephric patients showed, the metabolic clearance seems to be very low. No vancomycin metabolites have been identified so far in humans.

If vancomycin is given during a peritoneal dialysis via the intraperitoneal route, approx. 60% reaches the systemic circulation during 6 hours. After i.p. administration of 30 mg/kg BW, serum levels of approx. 10 mg/l are achieved.

In case of oral use, high-polar vancomycin is virtually not absorbed. It appears after oral administration in active form in the stool, and is therefore a suitable chemotherapeutic for pseudomembranous colitis and staphylococcal colitis.

Vancomycin diffuses readily across the placenta and is distributed into cord blood.

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 show negative results, 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/m²), 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. This may lead to chemical or physical instability if mixed with other substances. Therefore, each parenteral solution should be checked visually for precipitations and discoloration prior to use.

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

In case of combination therapy of vancomycin with other antibiotics/chemotherapeutics, the preparations should be administered separately.

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**

**Powder:**
3 years

**Reconstituted solution:**
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and 96 hours at 2-8°C.

**Further diluted solution:**
Solutions for infusion that are diluted to 5 mg/ml with 5% Glucose Injection or 0.9% Sodium Chloride Injection are chemically and physically stable in a refrigerator (2°C - 8°C) for 48 hours, or at 25°C for 24 hours.
Solutions for infusion that are diluted to 5 mg/ml with 5% Glucose Injection + 0.9% Sodium Chloride Injection are chemically and physically stable in refrigerator (2°C - 8°C) for 48 hours, or at 25°C for 24 hours.

From a microbiological point of view the medicinal product should be used immediately unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

**6.4 Special precautions for storage**

**Powder:**
Store below 25°C.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

**6.5 Nature and contents of container**

Colourless type I 15 ml glass vial, with a bromobutyl rubber stopper and an aluminium/plastic flip-off cap.

Pack sizes: 5 vials.

**6.6 Special precautions for disposal**

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

**Preparation of the reconstituted solution**

Dissolve Vancomycin 500 mg Powder for solution for infusion in 10 ml of sterile Water for injection

One ml of reconstituted solution contains 50 mg of vancomycin.

**Appearance of reconstituted solution**

After reconstitution the solution is clear and colorless to slightly yellowish brown without visible particles.

For storage conditions of the reconstituted medicinal product, see section 6.3.

**Preparation of final diluted Solution for infusion**

Reconstituted solutions containing 50 mg/ml of vancomycin should be further diluted.

**Suitable diluents are:**
- 5% Glucose Injection or
- 0.9% Sodium Chloride Injection or
- 5% Glucose Injection with 0.9% Sodium Chloride Injection.

**Intermittent infusion:**

Reconstituted solution containing 500 mg of vancomycin (50 mg/ml) must be diluted further with at least 100 ml diluent (to 5mg/ml).

The concentration of vancomycin in Solution for infusion should not exceed 5 mg/ml.
The desired dose should be administered slowly by intravenous use at a rate of no more than 10 mg/minute, for at least 60 minutes or even longer.

**Continuous infusion:**
This should be used only if treatment with an intermittent infusion is not possible. Dilute 1000 mg to 2000 mg of dissolved vancomycin in a sufficient amount of the above suitable diluent and administer it in the form of a drip infusion, so that the patient will receive the prescribed daily dose in 24 hours.

**Appearance of diluted solution**
After dilution the solution is clear and colorless without visible particles.

For storage conditions of the diluted medicinal product, see section 6.3.

Before administration, the reconstituted and diluted solutions should be inspected visually for particulate matter and discoloration. Only clear, and colorless solution free from particles should be used.

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

7. **MARKETING AUTHORISATION HOLDER**
Billev Pharma aps
Fuglebækgaard
Elmegårdsgade 1A, Tørslev
DK-3630 Jægerspris
Denmark

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 18585/0017

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
09/11/2009

10 **DATE OF REVISION OF THE TEXT**
09/11/2009
1 NAME OF THE MEDICINAL PRODUCT
Vancomycin 1000 mg, powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 1000 mg vancomycin (hydrochloride) equivalent to 1000,000 IU.

3 PHARMACEUTICAL FORM
Powder for solution for infusion.
White or almost white powder.

After reconstitution a solution is obtained with a pH of approximately 3.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Vancomycin solution, used intravenously is indicated in the therapy of severe, potentially life-threatening infections due to susceptible gram-positive microorganisms which cannot be treated with or failed to respond to other effective, less toxic antimicrobial medicinal products, such as penicillins and cephalosporins.

Vancomycin should be reserved for those cases where there is a specific indication, to minimize the chance of resistance emerging.

Vancomycin is useful in the treatment of the following severe infections caused by susceptible microorganisms (see section 5.1):
- endocarditis,
- infections of bones (osteomyelitis),
- pneumonia,
- soft-tissue infections.

Endocarditis caused by enterococci, *Streptococcus viridans* or *S. bovis* should be treated with a combination of vancomycin and an aminoglycoside.

Vancomycin may be used in certain patients who cannot tolerate penicillins and other beta-lactam antibiotics, in the antibiotic prophylaxis in case of high risk for bacterial endocarditis or perioperatively for major surgical procedures (e.g., cardiac and vascular procedures, etc).

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

4.2 Posology and method of administration
*Vancomycin powder for solution for infusion must be administered intravenously. Each dose should be administered at a rate not exceeding 10 mg/min or over a period of time of at least 60 minutes (whichever is longer).*
The dose should be individually adapted according to weight, age and renal function.

The following dosage regimens are recommended:

Patients with normal renal function

*Adults and adolescents above 12 years of age:*
*The recommended daily intravenous dose is 2000mg, divided into doses of 500mg every 6 hours or 1000mg every 12 hours.*

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 (gentamicin plus rifampin, gentamicin, streptomycin).
Enterococcal endocarditis is treated for 6 weeks with vancomycin in combination with an aminoglycoside – according to national recommendations.

Peri-operative prophylaxis: 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.

*Children one month to 12 years of age:*
The recommended intravenous dose is 10mg/kg, every 6 hours or 20 mg/kg every 12 hours.

*Infants and newborns:*
The recommended initial dose is 15 mg/kg, followed by 10 mg/kg every 12 hours during the first week of life and every 8 hours after that age and up to 1 month of age. Careful monitoring of serum concentration of vancomycin is recommended (see below).

**Elderly patients:**
Lower maintenance doses may be required due to the age-related reduction in renal function.

**Obese patients:**
Modification of the usual daily doses may be required.

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

**Patients with impaired renal function**
The dose must be adjusted in patients with impaired renal function and the following nomogram can serve as guidance. Careful monitoring of serum concentration of vancomycin is recommended (see below).

![Dosing nomogram for adults with impaired renal function](image)

In patients with mild or moderate renal failure, the starting dose must not be less than 15 mg/kg. In patients with severe renal failure, it is preferable to administer a maintenance dose between 250 mg and 1000 mg at a spacing of several days rather than administer lower daily doses.

Patients with anuria (with practically no renal function) should receive a dose of 15 mg/kg body weight until the therapeutic serum concentration is reached. The maintenance doses are 1.9 mg/kg body weight per 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 without any renal function, even under regular hemodialysis, the following dosage is also possible: Saturating dose 1000 mg, maintenance dose 1000 mg every 7 - 10 days.

If polysulfone membranes are used in haemodialysis (high flux dialysis), the half-life of vancomycin is reduced. An additional maintenance dose may be necessary in patients on regular haemodialysis.

**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.

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 – 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 requiring fluid restriction can 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 refer to chapter 6.6.

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

4.3 Contraindications
Hypersensitivity to vancomycin

4.4 Special warnings and precautions for use

Warnings:
In the presence of acute anuria or cochlear damage, vancomycin must be used only when absolutely necessary and if no other safer alternatives are available.

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).

Rapid bolus administration (i.e. over several minutes) may be associated with severe hypotension (including shock and rare 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 minimized 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.

Nephrotoxicity: vancomycin must be used with caution in patients with renal failure as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations. In the treatment of these patients and in those who are receiving concomitant treatment with other nephrotoxic active substances (i.e. aminoglycosides), serial tests of renal function must be performed and the appropriate dose regimens adhered to in order to reduce the risk of nephrotoxicity to a minimum (see section 4.2).

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. 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.

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 minimized 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.

Prolonged use of vancomycin may lead to superinfections with resistant microorganisms, therefore such patients should be regularly monitored. If superinfection occurs during therapy, appropriate measures should be taken. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including vancomycin, and may range in the severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of vancomycin. Antiperistaltics are contraindicated.

Regular monitoring of the blood levels of vancomycin is indicated in 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.

Doses should be titrated on the basis of serum levels. Blood levels should be monitored and renal function tests performed regularly. It is a general recommendation to monitor the concentrations 2-3 times weekly. 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.

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. The concomitant use of vancomycin and anaesthetic agents in children has been associated with erythema and anaphylactoid reactions. If the administration of vancomycin is required for surgical prophylaxis, it is advisable to administer the anaesthetic agents after completion of the vancomycin infusion.

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 nephrotoxic active substances particularly gentamycin, amphotericin B, streptomycin, neomycin, kanamycin, amikacin, tobramycin, viomycin, bacitracin, polymyxin B, colistin and cisplatin may potentiate the nephrotoxicity and/or ototoxicity of vancomycin and consequently requires careful monitoring of the patient. Because of synergic action (e.g. with gentamycin) in these cases the maximum dose of vancomycin has to be restricted to 500 mg every 8 hours.

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, foetus 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 other antibiotics have failed. Vancomycin should be cautiously 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 medicine for nursing mother, the decision should 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
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The adverse reactions listed below is 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).

The most common adverse reactions are phlebitis and pseudo-allergic reactions in connection with too rapid intravenous use of vancomycin.

Blood and the lymphatic system disorders
Rare (≥ 10,000 to ≤1/1,000): thrombocytopenia, neutropenia, agranulocytosis, eosinophilia.

Immune system disorders
Rare (≥ 10,000 to ≤1/1,000): anaphylactic reactions, hypersensitivity reactions.

Ear and labyrinth disorders
Uncommon (≥ 1,000 to ≤1/100): transient or permanent loss of hearing.
Rare (≥ 10,000 to ≤1/1,000): tinnitus, dizziness.

Cardiac disorders
Very rare (≤1/10,000): cardiac arrest.

Vascular disorders
Common (>1/100 to ≤1/10): decrease in blood pressure, thrombophlebitis.
Rare (≥ 10,000 to ≤1/1,000): vasculitis.

Respiratory, thoracic and medistinal disorders
Common (>1/100 to ≤1/10): dyspnoea, stridor.

Gastrointestinal disorders
Rare (≥ 10,000 to ≤1/1,000): nausea.
Very rare (≤1/10,000): pseudomembranous enterocolitis.

Skin and subcutaneous tissue disorders
Common (>1/100 to ≤1/10): exanthema and mucosal inflammation, pruritus, urticaria.
Very rare (≤1/10, 000): exfoliative dermatitis, Stevens-Johnson syndrome, Lyell’s syndrome, IgA induced bullous dermatitis.

Renal and urinary disorders
Common (>1/100 to ≤1/10): renal insufficiency manifested primarily by increased serum creatinine or serum urea concentrations.
Rare (≥ 10,000 to ≤1/1,000): interstitial nephritis, acute renal failure.

General disorders and administration site conditions
Common (>1/100 to ≤1/10): redness of the upper body and the face, pain and spasm of the chest and back muscles.
Rare (≥ 10,000 to ≤1/1,000): drug fever, shivering.

During or shortly after rapid infusion anaphylactic reactions may occur. The reactions abate when administration is stopped, generally between 20 minutes and 2 hours after having stopped administration.

Ototoxicity has primarily been reported in patients given high doses, or concomitant treatment with other ototoxic medicinal products, or with pre-existing reduction in kidney function or hearing."

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4.9 Overdose

Toxicity due to overdose has been reported. 500 mg IV to a child, 2 year 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

General properties

ATC classification
Pharmacotherapeutic group: glycopeptide antibacterials, ATC code: J01XA01.

Mode of action
Vancomycin is a glycopeptide antibiotic. Vancomycin has a bactericidal effect on proliferating germs by inhibiting the biosynthesis of the cell wall. In addition, it impairs the permeability of the bacterial cell membrane and RNA synthesis.

Mechanism(s) of resistance
Acquired resistance to glycopeptides is based on acquisition of various van gene complexes. Van genes have rarely been found in Staphylococcus aureus, where changes in cell wall structure result in “intermediate” susceptibility, which is most commonly heterogeneous. There is no cross-resistance between vancomycin and other antibiotics but cross-resistance with other glycopeptide antibiotics, such as teicoplanin, does occur. Secondary development of resistance during therapy is rare. In some countries, increasing cases of resistance are observed particularly in enterococci; multi-resistant strains of Enterococcus faecium are especially alarming.

Synergism
The combination of vancomycin with an aminoglycoside antibiotic has a synergistic effect against many strains of Staphylococcus aureus, non-enterococcal D-streptococci, enterococci and streptococci of the Viridans group. The combination of vancomycin with a cephalosporin has a synergistic effect against some oxacillin-resistant Staphylococcus epidermidis strains, and the combination of vancomycin with rifampicin has a synergistic effect against Staphylococcus epidermidis and a partial synergistic effect against some Staphylococcus aureus strains. As vancomycin in combination with a cephalosporin may also have an antagonistic effect against some Staphylococcus epidermidis strains and in combination with rifampicin against some Staphylococcus aureus strains, preceding synergism testing is useful. Specimens for bacterial cultures should be obtained in order to isolate and indentify the causative organisms and to determine their susceptibility to vancomycin.

Breakpoints
Minimum inhibitory concentration (MIC) breakpoint established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Staphylococcus spp. and Streptococcus spp. are Susceptible ≤ 2 mg/L and Resistant > 2 mg/L; for Enterococcus spp. are Susceptible ≤ 4 mg/L and Resistant > 4 mg/L; and for non-species related are Susceptible ≤ 2 mg/L and Resistant > 4 mg/L.

Susceptibility
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 is at least some types of infections is questionable.

Vancomycin has a narrow spectrum of action.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus spp</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
</tr>
</tbody>
</table>
5.2 Pharmacokinetic properties

- **Distribution:** Following intravenous administration, vancomycin is distributed to almost all tissues and diffuses in pleural, pericardial, ascitic and synovial fluid as well as in the cardiac muscle and in heart valves. Comparable high concentrations are achieved as in blood plasma. Data about the vancomycin concentrations in bone (spongiosa, compacta) vary widely. The apparent distribution volume in steady state is stated to be 0.43 (up to 0.9) L/kg. In non-inflamed meninges vancomycin passes the blood-brain barrier only to a low extent. Vancomycin is bound to plasma proteins at 30 to 55% and even higher.

- **Elimination:** Vancomycin is metabolized only to a low extent. After parenteral administration it is excreted almost completely as microbiologically active substance (approx. 75-90% within 24 hours) through glomerular filtration via the kidneys. Biliary excretion is insignificant (less than 5% of a dose).

In patients with normal renal function the half-life in serum is about 4-6 (5-11) hours, in children 2-2-3 hours. In impaired renal function, the half-life of vancomycin may be considerably prolonged (up to 7.5 days). Due to ototoxicity of vancomycin therapy-adjuvant monitoring of the plasma concentrations is indicated in such cases.

Mean plasma concentrations after i.v. infusion of 1000 mg vancomycin over 60 minutes were about 63 mg/L at the end of the infusion, about 23 mg/L after 2 hours and about 8 mg/L after 11 hours.

The clearance of vancomycin from plasma correlates nearly with the glomerular filtration rate.

The total systemic and renal clearance of vancomycin can be reduced in elderly patients.

As studies in anephric patients showed, the metabolic clearance seems to be very low. No vancomycin metabolites have been identified so far in humans.

If vancomycin is given during a peritoneal dialysis via the intraperitoneal route, approx. 60% reaches the systemic circulation during 6 hours. After i.p. administration of 30 mg/kg BW, serum levels of approx. 10 mg/l are achieved.

In case of oral use, high-polar vancomycin is virtually not absorbed. It appears after oral administration in active form in the stool, and is therefore a suitable chemotherapeutic for pseudomembranous colitis and staphylococcal colitis.

Vancomycin diffuses readily across the placenta and is distributed into cord blood.

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 show negative results, 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/m²), 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. This may lead to chemical or physical instability if mixed with other substances. Therefore, each parenteral solution should be checked visually for precipitations and discoloration prior to use.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
**Combination therapy**
In case of combination therapy of vancomycin with other antibiotics/chemotherapeutics, the preparations should be administered separately.

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**
Powder:
3 years

Reconstituted solution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and 96 hours at 2-8°C.

Further diluted solution:
Solutions for infusion that are diluted to 5 mg/ml with 5% Glucose Injection or 0.9% Sodium Chloride Injection are chemically and physically stable in a refrigerator (2°C - 8°C) for 48 hours, or at 25°C for 24 hours.
Solutions for infusion that are diluted to 5 mg/ml with 5% Glucose Injection + 0.9% Sodium Chloride Injection are chemically and physically stable in refrigerator (2°C - 8°C) for 48 hours, or at 25°C for 24 hours.

From a microbiological point of view the medicinal product should be used immediately unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 **Special precautions for storage**
Powder:
Store below 25°C.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 **Nature and contents of container**
Colourless type I 25 ml glass vial, with a bromobutyl rubber stopper and an aluminium/plastic flip-off cap.

Pack sizes: 1, 5, 10 and 100 vials.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
The product must be reconstituted and the resulting concentrate must then be diluted prior to use.

**Preparation of the reconstituted solution**
Dissolve Vancomycin 1000 mg Powder for solution for infusion in 20 ml of sterile Water for injection

One ml of reconstituted solution contains 50 mg of vancomycin.

**Appearance of reconstituted solution**
After reconstitution the solution is clear and colorless to slightly yellowish brown without visible particles.

For storage conditions of the reconstituted medicinal product, see section 6.3.

**Preparation of final diluted Solution for infusion**
Reconstituted solutions containing 50 mg/ml of vancomycin should be further diluted.
**Suitable diluents are:**
- 5% Glucose Injection
- 0.9% Sodium Chloride Injection
- 5% Glucose Injection with 0.9% Sodium Chloride Injection.

**Intermittent infusion:**
Reconstituted solution containing 1000 mg of vancomycin (50 mg/ml) must be diluted further with at least 200 ml diluent (to 5mg/ml).

The concentration of vancomycin in Solution for infusion should not exceed 5 mg/ml. The desired dose should be administered slowly by intravenous use at a rate of no more than 10 mg/minute, for at least 60 minutes or even longer.

**Continuous infusion:**
This should be used only if treatment with an intermittent infusion is not possible. Dilute 1000 mg to 2000 mg of dissolved vancomycin in a sufficient amount of the above suitable diluent and administer it in the form of a drip infusion, so that the patient will receive the prescribed daily dose in 24 hours.

**Appearance of diluted solution**
After dilution the solution is clear and colorless without visible particles.

For storage conditions of the diluted medicinal product, see section 6.3.

Before administration, the reconstituted and diluted solutions should be inspected visually for particulate matter and discoloration. Only clear, and colorless solution free from particles should be used.

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

7. **MARKETING AUTHORISATION HOLDER**
Billev Pharma aps
Fuglebækgaard
Elmegårdsvej 1A, Tørslev
DK-3630 Jægerspris
Denmark

8. **MARKETING AUTHORISATION NUMBER(S)**
PL 18585/0019

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
09/11/2009

10. **DATE OF REVISION OF THE TEXT**
09/11/2009
1 NAME OF THE MEDICINAL PRODUCT
Vancomycin hydrochloride 1000 mg, powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 1000 mg vancomycin (hydrochloride) equivalent to 1000,000 IU.

3 PHARMACEUTICAL FORM
Powder for solution for infusion.
White or almost white powder.

After reconstitution a solution is obtained with a pH of approximately 3.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Vancomycin solution, used intravenously is indicated in the therapy of severe, potentially life-threatening infections due to susceptible gram-positive microorganisms which cannot be treated with or failed to respond to other effective, less toxic antimicrobial medicinal products, such as penicillins and cephalosporins.

Vancomycin should be reserved for those cases where there is a specific indication, to minimize the chance of resistance emerging.

Vancomycin is useful in the treatment of the following severe infections caused by susceptible microorganisms (see section 5.1):
- endocarditis,
- infections of bones (osteomyelitis),
- pneumonia,
- soft-tissue infections.

Endocarditis caused by enterococci, Streptococcus viridans or S. bovis should be treated with a combination of vancomycin and an aminoglycoside.

Vancomycin may be used in certain patients who cannot tolerate penicillins and other beta-lactam antibiotics, in the antibiotic prophylaxis in case of high risk for bacterial endocarditis or perioperatively for major surgical procedures (e.g., cardiac and vascular procedures, etc).

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

4.2 Posology and method of administration
Vancomycin powder for solution for infusion must be administered intravenously. Each dose should be administered at a rate not exceeding 10 mg/min or over a period of time of at least 60 minutes (whichever is longer).

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

The following dosage regimens are recommended:

Patients with normal renal function

Adults and adolescents above 12 years of age:
The recommended daily intravenous dose is 2000mg, divided into doses of 500mg every 6 hours or 1000mg every 12 hours.

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 (gentamicin plus rifampin, gentamicin, streptomycin). Enterococcal endocarditis is treated for 6 weeks with vancomycin in combination with an aminoglycoside – according to national recommendations.

Peri-operative prophylaxis: 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.

Children one month to 12 years of age:
The recommended intravenous dose is 10mg/kg, every 6 hours or 20 mg/kg every 12 hours.

Infants and newborns:
The recommended initial dose is 15 mg/kg, followed by 10 mg/kg every 12 hours during the first week of life and every 8 hours after that age and up to 1 month of age. Careful monitoring of serum concentration of vancomycin is recommended (see below).

**Elderly patients:**
Lower maintenance doses may be required due to the age-related reduction in renal function.

**Obese patients:**
Modification of the usual daily doses may be required.

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

**Patients with impaired renal function**
The dose must be adjusted in patients with impaired renal function and the following nomogram can serve as guidance. Careful monitoring of serum concentration of vancomycin is recommended (see below).

![Dosing nomogram for adults with impaired renal function](image)

**Dosing nomogram for adults with impaired renal function**

In patients with mild or moderate renal failure, the starting dose must not be less than 15 mg/kg. In patients with severe renal failure, it is preferable to administer a maintenance dose between 250 mg and 1000 mg at a spacing of several days rather than administer lower daily doses.

Patients with *anuria* (with practically no renal function) should receive a dose of 15 mg/kg body weight until the therapeutic serum concentration is reached. The maintenance doses are 1.9 mg/kg body weight per 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 without any renal function, even under regular hemodialysis, the following dosage is also possible: Saturating dose 1000 mg, maintenance dose 1000 mg every 7 - 10 days.

If polysulfone membranes are used in haemodialysis (high flux dialysis), the half-life of vancomycin is reduced. An additional maintenance dose may be necessary in patients on regular haemodialysis.

**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.

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 10mg/min – over at least 60 min) which is sufficiently diluted (at least 100ml per 500mg or at least 200ml per 1000mg). Patients requiring fluid restriction can receive a solution of 500mg/50ml or 1000mg/100ml. With these higher concentrations the risk for infusion related side effects can be increased.

For information about the preparation of the solution, please refer to chapter 6.6.

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

4.3 Contraindications
Hypersensitivity to vancomycin

4.4 Special warnings and precautions for use

Warnings:
In the presence of acute anuria or cochlear damage, vancomycin must be used only when absolutely necessary and if no other safer alternatives are available.

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, corticosteroids, and – if necessary – artificial respiration).

Rapid bolus administration (i.e. over several minutes) may be associated with severe hypotension (including shock and rare 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 minimized 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.

Nephrotoxicity: vancomycin must be used with caution in patients with renal failure as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations. In the treatment of these patients and in those who are receiving concomitant treatment with other nephrotoxic active substances (i.e. aminoglycosides), serial tests of renal function must be performed and the appropriate dose regimens adhered to in order to reduce the risk of nephrotoxicity to a minimum (see section 4.2).

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. 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.

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 minimized 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.

Prolonged use of vancomycin may lead to superinfections with resistant microorganisms, therefore such patients should be regulatory monitored. If superinfection occurs during therapy, appropriate measures should be taken. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including vancomycin, and may range in the severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of vancomycin. Antiperistaltics are contraindicated.

Regular monitoring of the blood levels of vancomycin is indicated in 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.

Doses should be titrated on the basis of serum levels. Blood levels should be monitored and renal function tests performed regularly. It is a general recommendation to monitor the concentrations 2-3 times weekly. 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.

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. The concomitant use of vancomycin and anaesthetic agents in children has been associated with erythema and anaphylactoid reactions. If the administration of vancomycin is required for surgical prophylaxis, it is advisable to administer the anaesthetic agents after completion of the vancomycin infusion.

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 and cisplatin may potentiate the nephrotoxicity and/or ototoxicity of vancomycin and consequently requires careful monitoring of the patient.
Because of synergic action (e.g. with gentamycin) in these cases the maximum dose of vancomycin has to be restricted to 500 mg every 8 hours.

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, foetus 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 other antibiotics have failed. Vancomycin should be cautiously 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 medicine for nursing mother, the decision should 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
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The adverse reactions listed below is 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).

The most common adverse reactions are phlebitis and pseudo-allergic reactions in connection with too rapid intravenous use of vancomycin.

Blood and the lymphatic system disorders
*Rare* (≥ 10,000 to ≤ 1/1,000): thrombocytopenia, neutropenia, agranulocytosis, eosinophilia.

Immune system disorders
*Rare* (≥ 10,000 to ≤ 1/1,000): anaphylactic reactions, hypersensitivity reactions.

Ear and labyrinth disorders
*Uncommon* (≥ 1,000 to ≤ 1/100): transient or permanent loss of hearing.
*Rare* (≥ 10,000 to ≤ 1/1,000): tinnitus, dizziness.

Cardiac disorders
*Very rare* (≤ 1/10,000): cardiac arrest.

Vascular disorders
*Common* (>1/100 to ≤ 1/10): decrease in blood pressure, thrombophlebitis.
*Rare* (≥ 10,000 to ≤ 1/1,000): vasculitis.

Respiratory, thoracic and mediastinal disorders
*Common (>1/100 to ≤ 1/10):* dyspnoea, stridor.

Gastrointestinal disorders
*Rare* (≥ 10,000 to ≤ 1/1,000): nausea.
*Very rare* (≤ 1/10,000): pseudomembranous enterocolitis.

Skin and subcutaneous tissue disorders
*Common* (>1/100 to ≤ 1/10): exanthema and mucosal inflammation, pruritus, urticaria.
*Very rare* (≤ 1/10, 000): exfoliative dermatitis, Stevens-Johnson syndrome, Lyell’s syndrome, IgA induced bullous dermatitis.

Renal and urinary disorders
*Common* (>1/100 to ≤ 1/10): renal insufficiency manifested primarily by increased serum creatinine or serum urea concentrations.
*Rare* (≥ 10,000 to ≤ 1/1,000): interstitial nephritis, acute renal failure.

General disorders and administration site conditions
*Common* (>1/100 to ≤ 1/10): redness of the upper body and the face, pain and spasm of the chest and back muscles.
*Rare* (≥ 10,000 to ≤ 1/1,000): drug fever, shivering.

During or shortly after rapid infusion anaphylactic reactions may occur. The reactions abate when administration is stopped, generally between 20 minutes and 2 hours after having stopped administration.

"Ototoxicity has primarily been reported in patients given high doses, or concomitant treatment with other ototoxic medicinal products, or with pre-existing reduction in kidney function or hearing."
4.9 Overdose
Toxicity due to overdose has been reported. 500 mg IV to a child, 2 year 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

General properties
ATC classification
Pharmacotherapeutic group: glycopeptide antibacterials, ATC code: J01XA01.

Mode of action
Vancomycin is a glycopeptide antibiotic. Vancomycin has a bactericidal effect on proliferating germs by inhibiting the biosynthesis of the cell wall. In addition, it impairs the permeability of the bacterial cell membrane and RNA synthesis.

Mechanism(s) of resistance
Acquired resistance to glycopeptides is based on acquisition of various van gene complexes. Van genes have rarely been found in Staphylococcus aureus, where changes in cell wall structure result in “intermediate” susceptibility, which is most commonly heterogeneous.
There is no cross-resistance between vancomycin and other antibiotics but cross-resistance with other glycopeptide antibiotics, such as teicoplanin, does occur. Secondary development of resistance during therapy is rare.
In some countries, increasing cases of resistance are observed particularly in enterococci; multi-resistant strains of Enterococcus faecium are especially alarming.

Synergism
The combination of vancomycin with an aminoglycoside antibiotic has a synergistic effect against many strains of Staphylococcus aureus, non-enterococcal D-streptococci, enterococci and streptococci of the Viridans group. The combination of vancomycin with a cephalosporin has a synergistic effect against some oxacillin-resistant Staphylococcus epidermidis strains, and the combination of vancomycin with rifampicin has a synergistic effect against Staphylococcus epidermidis and a partial synergistic effect against some Staphylococcus aureus strains. As vancomycin in combination with a cephalosporin may also have an antagonistic effect against some Staphylococcus epidermidis strains and in combination with rifampicin against some Staphylococcus aureus strains, preceding synergism testing is useful.
Specimens for bacterial cultures should be obtained in order to isolate and indentify the causative organisms and to determine their susceptibility to vancomycin.

Breakpoints
Minimum inhibitory concentration (MIC) breakpoint established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Staphylococcus spp. and Streptococcus spp. are Susceptible ≤ 2 mg/L and Resistant > 2 mg/L; for Enterococcus spp. are Susceptible ≤ 4 mg/L and Resistant > 4 mg/L; and for non-species related are Susceptible ≤ 2 mg/L and Resistant > 4 mg/L.

Susceptibility
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 is at least some types of infections is questionable.
Vancomycin has a narrow spectrum of action.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus spp</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
</tr>
</tbody>
</table>
5.2 Pharmacokinetic properties

- **Distribution:** Following intravenous administration, vancomycin is distributed to almost all tissues and diffuses in pleural, pericardial, ascitic and synovial fluid as well as in the cardiac muscle and in heart valves. Comparable high concentrations are achieved as in blood plasma. Data about the vancomycin concentrations in bone (spongiosa, compacta) vary widely. The apparent distribution volume in steady state is stated to be 0.43 (up to 0.9) L/kg. In non-inflamed meninges vancomycin passes the blood-brain barrier only to a low extent. Vancomycin is bound to plasma proteins at 30 to 55 % and even higher.

- **Elimination:** Vancomycin is metabolized only to a low extent. After parenteral administration it is excreted almost completely as microbiologically active substance (approx. 75-90% within 24 hours) through glomerular filtration via the kidneys. Biliary excretion is insignificant (less than 5% of a dose).

In patients with normal renal function the half-life in serum is about 4-6 (5-11) hours, in children 2.2-3 hours. In impaired renal function, the half-life of vancomycin may be considerably prolonged (up to 7.5 days). Due to ototoxicity of vancomycin therapy-adjuvant monitoring of the plasma concentrations is indicated in such cases.

Mean plasma concentrations after i.v. infusion of 1000 mg vancomycin over 60 minutes were about 63 mg/L at the end of the infusion, about 23 mg/L after 2 hours and about 8 mg/L after 11 hours.

The clearance of vancomycin from plasma correlates nearly with the glomerular filtration rate.

The total systemic and renal clearance of vancomycin can be reduced in elderly patients.

As studies in anephric patients showed, the metabolic clearance seems to be very low. No vancomycin metabolites have been identified so far in humans.

If vancomycin is given during a peritoneal dialysis via the intraperitoneal route, approx. 60% reaches the systemic circulation during 6 hours. After i.p. administration of 30 mg/kg BW, serum levels of approx. 10 mg/l are achieved.

In case of oral use, high-polar vancomycin is virtually not absorbed. It appears after oral administration in active form in the stool, and is therefore a suitable chemotherapeutic for pseudomembranous colitis and staphylococcal colitis.

Vancomycin diffuses readily across the placenta and is distributed into cord blood.

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 show negative results, 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/m²), 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. This may lead to chemical or physical instability if mixed with other substances. Therefore, each parenteral solution should be checked visually for precipitations and discoloration prior to use.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
**Combination therapy**
In case of combination therapy of vancomycin with other antibiotics/chemotherapeutics, the preparations should be administered separately.

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**
Powder:
3 years

Reconstituted solution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and 96 hours at 2-8°C.

Further diluted solution:
Solutions for infusion that are diluted to 5 mg/ml with 5% Glucose Injection or 0.9% Sodium Chloride Injection are chemically and physically stable in a refrigerator (2°C - 8°C) for 48 hours, or at 25°C for 24 hours.
Solutions for infusion that are diluted to 5 mg/ml with 5% Glucose Injection + 0.9% Sodium Chloride Injection are chemically and physically stable in refrigerator (2°C - 8°C) for 48 hours, or at 25°C for 24 hours.

From a microbiological point of view the medicinal product should be used immediately unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 **Special precautions for storage**
Powder:
Store below 25°C.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 **Nature and contents of container**
Colourless type I 25 ml glass vial, with a bromobutyl rubber stopper and an aluminium/plastic flip-off cap.

Pack sizes: 5 vials.

6.6 **Special precautions for disposal**
The product must be reconstituted and the resulting concentrate must then be diluted prior to use.

**Preparation of the reconstituted solution**
Dissolve Vancomycin 1000 mg Powder for solution for infusion in 20 ml of sterile Water for injection

One ml of reconstituted solution contains 50 mg of vancomycin.

**Appearance of reconstituted solution**
After reconstitution the solution is clear and colorless to slightly yellowish brown without visible particles.

For storage conditions of the reconstituted medicinal product, see section 6.3.

**Preparation of final diluted Solution for infusion**
Reconstituted solutions containing 50 mg/ml of vancomycin should be further diluted.

*Suitable diluents are:*
- 5% Glucose Injection or
- 0.9% Sodium Chloride Injection or
- 5% Glucose Injection with 0.9% Sodium Chloride Injection.

**Intermittent infusion:**
Reconstituted solution containing 1000 mg of vancomycin (50 mg/ml) must be diluted further with at least 200 ml diluent (to 5mg/ml).
The concentration of vancomycin in Solution for infusion should not exceed 5 mg/ml. The desired dose should be administered slowly by intravenous use at a rate of no more than 10 mg/minute, for at least 60 minutes or even longer.

*Continuous infusion:* This should be used only if treatment with an intermittent infusion is not possible. Dilute 1000 mg to 2000 mg of dissolved vancomycin in a sufficient amount of the above suitable diluent and administer it in the form of a drip infusion, so that the patient will receive the prescribed daily dose in 24 hours.

**Appearance of diluted solution**
After dilution the solution is clear and colorless without visible particles.

For storage conditions of the diluted medicinal product, see section 6.3.

Before administration, the reconstituted and diluted solutions should be inspected visually for particulate matter and discoloration. Only clear, and colorless solution free from particles should be used.

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

7. **MARKETING AUTHORIZATION HOLDER**
Billev Pharma aps
Fuglebækgård
Elmegårdsvej 1A, Tørslev
DK-3630 Jægerspris
Denmark

8. **MARKETING AUTHORIZATION NUMBER(S)**
PL 18585/0020

9. **DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**
09/11/2009

10. **DATE OF REVISION OF THE TEXT**
09/11/2009
Module 3
Patient Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Vancomycin 500 mg, powder for solution for infusion
Vancomycin 1000 mg, powder for solution for infusion

Vancomycin

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Vancomycin is and what it is used for
2. Before you are given Vancomycin
3. How you are given Vancomycin
4. Possible side effects
5. How to store Vancomycin
6. Further information

1 What Vancomycin is and what it is used for

Vancomycin belongs to a group of glycopeptide antibiotics which eliminate bacteria that cause many kinds of infections, including pneumonia and skin, bone and heart valve infections. It is used to treat:
- serious infections caused by vancomycin-sensitive bacteria which are resistant (insensitive) to many other antibiotics,
- patients allergic to penicillins and cephalosporins.

It can also be given to you before some surgical procedures to prevent infections.

Your medicine is in the form of a powder for solution. Before use, it will be dissolved and diluted with an intravenous fluid that will be given to you slowly by a drip into your vein by a doctor or nurse.

2 Before you are given Vancomycin

be determined periodically and periodic testing of hearing function is recommended.

If you will receive vancomycin over a longer-term period, your blood will be tested at regular intervals. You should also be monitored because of possible superinfection (new infection occurring over the existing one) or severe, sometimes bloody diarrhoea (condition called pseudomembranous colitis).

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, herbal remedies or vitamins and minerals, because some of them could have an interaction with vancomycin. Furthermore, do not take any new medicine without consulting your doctor.

The following can react with vancomycin if you take them at the same time, such as medicines for the treatment of:
- infections caused by bacteria
  (streptomycin, neomycin, gentamicin, kanamycin, amikacin, bacitracin, tobramycin, polymixin B. colistin).
Do not have Vancomycin if you:
• are allergic (hypersensitive) to vancomycin.

Tell your doctor if you have had any problems with this medicine or any other in the past.

Take special care with Vancomycin
Before treatment with vancomycin, make sure that your doctor knows about your medical history, especially if you:
• have kidney problems
• have ear problems such as deafness
• have low blood count
• are pregnant, or planning to become pregnant
• are breastfeeding
• are elderly and over 60 years of age
• are a premature infant or a child
• are going to have surgery

In case you develop severe allergic reaction, your doctor will stop treatment with vancomycin and give you other appropriate treatment.
If you will be given the infusion too fast, you can get some side effects like low blood pressure or rash. Stopping the infusion usually results in a prompt cessation of these reactions.

Vancomycin must be used with caution in patients with kidney failure or in those who receive concomitant treatment with other substances toxic to kidney as the possibility of developing toxic effects is much higher. Serial tests of kidney function should be performed and the appropriate dose regimens adhered to in order to reduce this risk.

Deafness, transitory or permanent, which may be preceded by noises in ears, can occur in patients with prior deafness, who have received excessive doses, or who receive concomitant treatment with another substance toxic to hearing. To reduce this risk, blood levels should

• tuberculosis (vomycin),
• fungal infections (amphotericin B),
• cancer (cisplatin),
and:
• medicines for muscle relaxation during anaesthesia,
• anaesthetic agents (if you are going to have general anaesthesia).

Your doctor may need to monitor your blood and adjust the dosage if vancomycin is given at the same time with other medicines.

Pregnancy and breast-feeding
Pregnancy
If you are, or think you may be, pregnant, tell your doctor. Vancomycin should be given during pregnancy only if clearly needed.

Breast-feeding
Tell your doctor if you are breast-feeding as Vancomycin passes into breast milk. Your doctor will decide, if vancomycin is clearly needed or if you must stop breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Vancomycin has no or very little effect on your ability to drive and operate machines.

3 How you are given Vancomycin

You will be given Vancomycin by medical staff while you are in hospital.
Your doctor will decide how much of this medicine you should receive each day and how long the treatment will last.

Continued on the next page >>
The following information is intended for medical or healthcare professionals only:

This is an extract from the Summary of Product Characteristics to assist in the administration of Vancomycin. When determining appropriateness of use in a particular patient, the prescriber should be familiar with the Summary of Product Characteristics of the medicinal product.

Dosage and method of administration

Vancomycin is administered via an intravenous infusion and not in the form of a bolus injection or intramuscularly.

Adults and adolescents above 12 years of age

The recommended daily intravenous dose is 2 g, divided into doses of 500 mg every 6 hours or 1000 mg every 12 hours.

Parenterally vancomycin shall only be administered as slow intravenous infusion (not more than 10 mg/min – 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 requiring fluid restriction can 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 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 (gentamicin plus rifampin, gentamicin, streptomycin). Enterococcal endocarditis is treated for 6 weeks with vancomycin in combination with an aminoglycoside – according to national recommendations.

Peri-operative prophylaxis:

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.

Children one month to 12 years of age

The recommended intravenous dose is 10 mg/kg, every 6 hours or 20 mg/kg every 12 hours.
Infants and newborns
The recommended initial dose is 15 mg/kg, followed by 10 mg/kg every 12 hours during the first week of life and every 8 hours after that age and up to 1 month of age. Careful monitoring of serum concentration of vancomycin is recommended (see below).

Elderly patients:
Lower maintenance doses may be required due to the age-related reduction in renal function.

Obese patients:
Modification of the usual daily doses may be required.

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

Patients with impaired renal function
The dose must be adjusted in patients with impaired renal function and the following nomogram can serve as guidance. Careful monitoring of serum concentration of vancomycin is recommended (see below).

In patients with mild or moderate renal failure, the starting dose must not be less than 15 mg/kg. In patients with severe renal failure, it is preferable to administer a maintenance dose between 250 mg and 1000 mg at a spacing of several days rather than administer lower daily doses.

Continued on the next page >>
Dosage
The dose given to you will depend on
- your age,
- the infection you have,
- how well your kidneys are working,
- your hearing ability
- any other medicines you may be taking.

Adults and children above 12 years:
the usual dose is 2000 mg daily in two or four doses.

Children under 12 years:
will be given smaller doses, depending on their body weight.

Patients with impaired kidney function, the elderly and pre-term new-born infants:
the doctor will reduce the dose or extend the interval between two doses.

During treatment you might have blood tests, be asked to provide urine samples and possibly have hearing tests to look for signs of possible side effects.

How the treatment will be given
Intravenous infusion means that the medicinal product flows from an infusion bottle or bag through a tube to one of your blood vessels and into your body. Your doctor, or nurse, will always give vancomycin into your blood, never in a muscle. Vancomycin will be diluted before being given to you, and will slowly flow into your vein for at least 60 minutes.

Duration of treatment
The length of treatment depends on the infection you have and may last a number of weeks.

- noises (e.g. hissing) in ears;
- feeling faint;
- red or purple skin (possible signs of blood vessel inflammation);
- nausea.

Very rare side effects (affect less than 1 user in 10,000):
Skin disorders resulting from an allergic reaction (multiple skin lesions, joint aches), cardiac arrest, or inflammation of the bowel which causes abdominal pain or bloody diarrhoea.

If any of the side effects get serious, or if you notice any side effects not mentioned in this leaflet, please tell your doctor.

How to store Vancomycin
Your doctor or nurse will ensure that Vancomycin is properly stored.

Keep out the reach and sight of children.

Do not use this medicine after the expiry date which is stated on the vial label and the carton. Do not store above 25°C.

The stability of reconstituted solution is stated below in the additional information for health professionals.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
If you are given more Vancomycin than you should
As this medicine will be given to you while you are in the hospital, it is unlikely that you will be given too much vancomycin. However, tell your doctor or nurse immediately if you have any concerns.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 Possible side effects
Like all medicines, Vancomycin can cause side effects, although not everybody gets them.

Stop taking the medicine immediately and seek medical attention if signs of an allergic reaction occur:
- hives; swelling of your face, lips, tongue, or throat; difficulty breathing or swallowing or dizziness.

If you think you have any of the following side effects or symptoms, tell your doctor as soon as possible:

Common side effects (affect 1 to 10 users in 100):
- decrease in blood pressure; swelling, redness and pain along a vein;
- breathlessness, a high pitched sound resulting from turbulent air flow in the upper airway;
- generalized rash and mucosal inflammation, itching, itchy rash;
- redness of the upper body and the face, pain and spasm of the chest and back muscles;
- kidney problems which may be detected primarily by increased creatinine or urea concentrations in your blood.

Uncommon side effects (affect 1 to 10 users in 1,000):
- temporary or permanent loss of hearing.

Rare side effects (affect 1 to 10 users in 10,000):
- anaphylactic reactions, allergic reactions;
- drug fever, chills;
- increased or reduced (sometimes severely decreased) urine output, or traces of blood in urine;
- increase or decrease in some of the cells in the blood;

6 Further information
What Vancomycin contains
- The active substance is vancomycin hydrochloride.

Vancomycin 500 mg, powder for solution for infusion:
Each vial contains 500 mg vancomycin (hydrochloride) equivalent to 500,000 IU.

Vancomycin 1000 mg, powder for solution for infusion:
Each vial contains 1000 mg vancomycin (hydrochloride) equivalent to 1,000,000 IU.

There are no other ingredients.

What Vancomycin looks like and contents of the pack
Vancomycin is a white or almost white freeze-dried powder for solution for intravenous infusion. It must be first dissolved in water for injection and further diluted in an appropriate diluent prior to use.

This medicine is supplied in colourless glass vials closed with rubber closures and sealed with aluminium and plastic flip off caps. This medicine is available in two strengths: 500 mg and 1000 mg.

Vancomycin is packed in carton boxes. Each box can contain 1, 5, 10 or 100 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Billeb Pharma aps, Fuglebakgaard,
Elnegårdsvej 1A, Taravej, DK-3630 Jægerspris, Denmark.

Manufacturer:
Lek Pharmaceuticals d.d., Verovškova 57, 1526 Ljubljana, Slovenia.

This leaflet was last approved in 10/2009 (to be amended after approval)
Patients with anuria (with practically no renal function) should receive a dose of 15 mg/kg body weight until the therapeutic serum concentration is reached. The maintenance doses are 1.9 mg/kg body weight per 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.

Preparation of infusion solution

For a 500 mg dose, dissolve 500 mg of vancomycin in 10 ml of water for injections.
For a 1000 mg dose, dissolve 1000 mg of vancomycin in 20 ml of water for injections.
One ml of reconstituted solution contains 50 mg of vancomycin. Solution prepared aseptically in this manner may be stored for 24 hours at 25°C or for 96 hours in a refrigerator at between 2°C and 8°C. After reconstitution, this solution should be further diluted.
The suitable diluents for further dilution are:
- 5% Glucose Injection or
- 0.9% Sodium Chloride Injection or
- 5% Glucose Injection with 0.9% Sodium Chloride Injection.

Intermittent infusion: Reconstituted solution containing 500 mg of vancomycin (50 mg/ml) must be diluted further with at least 100 ml of the above diluent (to 5mg/ml).
Reconstituted solution containing 1000 mg vancomycin (50 mg/ml) must be diluted further with at least 200 ml of the above diluent (to 5mg/ml).
The concentration of vancomycin in solution for infusion should not exceed 5 mg/ml.

Stability of diluted solutions

Vancomycin reconstituted solution (50 mg/ml), further diluted with 5% glucose or 0.9% sodium chloride (5mg/ml) may be stored in a refrigerator for 48 hours, or at 25°C for 24 hours without significant loss of potency. Solutions diluted with a combination of 5% glucose and 0.9% sodium chloride may be stored in a refrigerator (2°C - 8°C) for 48 hours or at 25°C for 24 hours.

From a microbiological point of view the medicinal product should be used immediately unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Appearance of reconstituted solution
After reconstitution the solution is clear and colorless to slightly yellowish brown without visible particles.

Appearance of diluted solution
After dilution the solution is clear and colorless without visible particles.

Before administration, the reconstituted and diluted solutions should be inspected visually for particulate matter and discoloration. Only clear and colorless solution free from particles should be used.
Monitoring of 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. The concentrations should normally be monitored twice or three times per week.

Incompatibilities

The solution of vancomycin has a low pH value. In combination with other substances, it may become physically or chemically unstable.
Vancomycin solution should not be mixed with other solutions, with exceptions of those whose compatibility has been reliably verified.

Combination therapy:

In case of combination therapy of vancomycin with other antibiotic or chemotherapeutic agent, the preparations should be administered separately.

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.

Disposal

Vials are for single use only. Unused medicinal product must be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Module 4
Labelling

For single use only. For intravenous infusion. Read the package leaflet before use. Do not store above 25°C. Must be reconstituted and diluted before use. Do not use unless the prepared solution is clear and colourless without visible particles. Keep out of the reach and sight of children.

Each vial contains 500 mg vancomycin (hydrochloride) equivalent to 500 000 IU.

When reconstituted with 10 ml water for injection, each ml contains 50 mg vancomycin.

Product Licence Number: PL 18368/0016

Beier Pharma aps, Fuglebjergvej, 1A, Taeler, DK-3630 Jægerspris, Denmark.

Vancomycin 500 mg Powder for solution for infusion

For single use only. For intravenous infusion after reconstitution and dilution. Do not store above 25°C. Do not use unless the prepared solution is clear and colourless without visible particles.

Keep out of the reach and sight of children. Each vial contains 500 mg vancomycin (hydrochloride) equivalent to 500 000 IU.

Product Licence Number: PL 18265/0016

Beier Pharma aps, Fuglebjergvej, 1A, Taeler, DK-3630 Jægerspris, Denmark.
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton box for vial(s)

1. NAME OF THE MEDICINAL PRODUCT

Vancomycin hydrochloride, 500 mg, powder for solution for infusion
Vancomycin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 500 mg vancomycin (hydrochloride) equivalent to 500 000 IU.

When reconstituted with 10 ml water for injections, each ml contains 50 mg vancomycin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion

1x5 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
For intravenous infusion.
Must be reconstituted and further diluted before use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use unless the prepared solution is clear and colorless without visible particles.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Billev Pharma aps
Fuglebækgaard
Elmegårdsvej 1A, Tønslev
DK-3630 Jægerspris
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

PL 18585/0017

13. MANUFACTURER’S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

N/A
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton box for vial(s)

1. NAME OF THE MEDICINAL PRODUCT

Vancomycin hydrochloride, 1000 mg, powder for solution for infusion
Vancomycin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 1000 mg vancomycin (hydrochloride) equivalent to 1000 000 IU.

When reconstituted with 20 ml water for injections, each ml contains 50 mg vancomycin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion

1x5 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
For intravenous infusion.
Must be reconstituted and further diluted before use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
Do not use unless the prepared solution is clear and colorless without visible particles.

8. **EXPIRY DATE**

   EXP

9. **SPECIAL STORAGE CONDITIONS**

   Do not store above 25°C.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

   Billev Pharma aps
   Fuglebækgaard
   Elmegårdsvej 1A, Torslev
   DK-3630 Jægerspris
   Denmark

12. **MARKETING AUTHORISATION NUMBER(S)**

   PL 18585/0020

13. **MANUFACTURER’S BATCH NUMBER**

   Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   POM

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

   N/A
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

**Vial**

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1. **NAME OF THE MEDICINAL PRODUCT**

Vancomycin, 1000 mg, powder for solution for infusion

**Vancomycin**

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2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 1000 mg vancomycin (hydrochloride) equivalent to 1000 000 IU.

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3. **LIST OF EXCIPIENTS**

---

4. **PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for infusion

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5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For single use only.
For intravenous infusion after reconstitution and dilution.

Read the package leaflet before use

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6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

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7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

Do not use unless the prepared solution is clear and colorless without visible particles.

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8. **EXPIRY DATE**

**EXP**
9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the MHRA have granted marketing authorisations to Billev Pharma APS for the products Vancomycin 500mg and 1000mg Powder for Solution for Infusion. These products are indicated in the therapy of severe, potentially life-threatening infections due to susceptible gram-positive microorganisms which cannot be treated with or failed to respond to other effective, less toxic antimicrobial medicinal products, such as penicillins and cephalosporins.

These are applications made under Article 10.1 of Directive 2001/83 EC for Vancomycin 500mg and 1000mg Powder for Solution for Infusion, claiming to be generic medicinal products of Vancocin 500 and 1000 mg powder for solution for infusion and oral solution, granted since 15 April 1990 and currently marketed by Flynn Pharma Limited. Vancomycin 500mg and 1000mg Powder for Solution for Infusion are prescription-only medicines.

With the UK as Reference Member State in these Decentralised Procedures (DCP), the marketing authorisation holder (Billev Pharma APS) gained approval in LV, IT, FI, ES, NL, EE, DK, CZ, BG, BE, SK, SI, SE, PT, DE, LU and PL, with the end of procedure (Day 210) on 15th October 2009.

For those CMS: EE, LV, PT, SI and SK where no originator product is registered, reference is made to the UK reference product. The application for the 1000 mg strength is submitted as a hybrid under Article 10(3) in CZ and IT due to change in strength of the active substance.

Vancomycin is a tricyclic glycopeptide bactericidal antibiotic. It acts by inhibiting the biosynthesis of the bacterial cell-wall; additionally, vancomycin alters bacterial-cell-membrane permeability and ribonucleic acid (RNA) synthesis. Vancomycin has a narrow spectrum of action. Parenteral administration of vancomycin is indicated for the treatment of serious, potentially life threatening infections, caused by susceptible gram-positive microorganisms resistant to other antimicrobial medicinal products, such as penicillins and cephalosporins, as well as in patients with known allergy to them:
- Endocarditis
- Infections of bones (osteomyelitis)
- Pneumonia
- Soft tissue infections

Vancomycin may be used in certain patients in antibiotic prophylaxis in case of high risk for bacterial endocarditis or perioperatively for major surgical procedures.

No new preclinical or clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

The RMS has also been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation. For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of
the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The marketing authorisation holder has provided justification for non submission of the Risk Management Plan.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Vancomycin 500mg and 1000mg Powder for Solution for Infusion Vancomycin hydrochloride 500mg and 1000mg Powder for Solution for Infusion |
| Name(s) of the active substance(s) (INN) | Vancomycin hydrochloride |
| Pharmacotherapeutic classification (ATC code) | Glycopeptide antibacterials J01XA |
| Pharmaceutical form and strength(s) | 500mg and 1000mg Powder for Solution for Infusion |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1383-4/01-2/DC |
| Reference Member State | United Kingdom |
| Member States concerned | LV, IT, FI, ES, NL, EE, DK, CZ, BG, BE, SK, SI, SE, PT DE, LU and PL |
| Marketing Authorisation Number(s) | PL 18585/0016-7, 0019-20 |
| Name and address of the authorisation holder | Billev Pharma APS, Fuglebaekgaard, Elmegardsvej 1A, DK-3630 Jaegerspris, Denmark |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

DRUG SUBSTANCE

INN: Vancomycin Hydrochloride


Structure:

Molecular Formula: C_{66}H_{76}Cl_{3}N_{9}O_{24}

Molecular Weight: 1486 g/mol

Appearance: white or almost white powder, hygroscopic, freely soluble in water, slightly soluble in alcohol.
**DRUG PRODUCT**

**Other ingredients**

Other ingredient consists of the pharmaceutical excipient Nitrogen.

This excipient complies with its respective European Pharmacopoeia monograph. A satisfactory Certificate of Analysis has been provided. Nitrogen contains no material of animal or human origin.

**Pharmaceutical Development**

Suitable pharmaceutical development data have been provided for these applications.

The physico-chemical properties of the drug product have been compared with those of the originator product. These data demonstrate that the proposed products can be considered generic medicinal products of Vancocin 500 and 1000 mg powder for solution for infusion and oral solution.

**Manufacture**

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

**Finished Product specification**

The Finished Product Specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**

The finished product is packed in colourless Type I glass vials with bromobutyl rubber stoppers and aluminium/plastic flip-off caps.

Pack sizes are 1, 5, 10 and 100 vials.

The marketing authorisation holder has stated that not all pack sizes may be marketed, however, they have committed to submitting any mock-ups to the Regulatory Authority for approval before marketing any pack size.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with guidelines concerning materials in contact with parenteral products.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years has been set for the unopened product, with the storage instructions ‘Store below 25 degree C’.
Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

The requirements for generic products of the proposed and originator products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar physico-chemical properties have been demonstrated for the proposed and originator products.

III.2 PRE-CLINICAL ASPECTS
These applications claim to be generic medicinal products of Vancocin 500 and 1000 mg powder for solution for infusion and oral solution, which have been licensed within the EU for over 10 years.

No new preclinical data have been supplied with these applications. However, a preclinical expert report summarising relevant non-clinical studies has been included in the dossier. This is satisfactory.

III.3 CLINICAL ASPECTS
III.3.1 Clinical Pharmacology
No new data have been submitted and none are required.

No bioequivalence study has been submitted. As these are powders for solution for infusion, no bioequivalence study is required.

III.3.2 Clinical Efficacy
No new data have been submitted and none are required.

III.3.3 Clinical Safety
No new data have been submitted and none are required.

Module 1 – Administrative information
MAA forms
The MAA forms are medically satisfactory.

Summary of Product Characteristics (SPC)
The SPCs are medically satisfactory and consistent with those for the reference products.

Patient Information Leaflet (PIL)
The PIL is medically satisfactory and consistent with the SPC.

Packaging
The packagings are medically satisfactory.

Module 2 – Clinical overall summary
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of Module 5.

Conclusions on safety
The medical assessor recommended that Marketing Authorisations were granted for these products.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Vancomycin 500mg and 1000mg Powder for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical studies were conducted. The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Vancocin 500 and 1000 mg powder for solution for infusion and oral solution beyond the already well-described effects of vancomycin hydrochloride.

EFFICACY
No new or unexpected safety concerns arise from these applications.

The SPC and PIL are satisfactory and consistent with those of the reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with vancomycin hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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