**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

**VancoAvenir 500 mg, powder for solution for injection.**

**VancoAvenir 1 g, powder for solution for injection.**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**VancoAvenir** 500 mg, powder for solution for injection.

Each vial contains vancomycin (as hydrochloride), 500 mg.
It contains no excipients.

**VancoAvenir** 1 g, powder for solution for injection.

Each vial contains vancomycin (as hydrochloride), 1 g.
It contains no excipients.

## 3. PHARMACEUTICAL FORM

Powder for solution for injection.
A white or almost white lyophilised powder in a clear vial with grey stopper.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Vancomycin hydrochloride is indicated for the treatment of severe or serious infections due to susceptible strains of methicillin - resistant (beta-lactam-resistant) staphylococci.
It is also indicated for administration to penicillin-allergic patients as well patients who have failed to respond to or who cannot receive other drugs including cephalosporins or penicillins and for infections due to vancomycin-susceptible organisms that are resistant to other antimicrobial drugs.
Vancomycin hydrochloride is indicated for first-line therapy when methicillin-resistant staphylococci are suspected but when susceptibility data become available appropriate therapy should be instituted.
Vancomycin hydrochloride is effective in the treatment of staphylococcal endocarditis as well as in other infections due to staphylococci including lower respiratory tract infections septicemia skin and skin - stucture infection and bone infections.
Antibiotic therapy is as an adjunct to appropriate surgical measures when staphylococcal infections are purulent and localized.
For endocarditis due to Streptococcus viridans or Streptococcus bovis vancomycin hydrochloride has been shown to be effective in combination with an aminoglycoside.
Vancomycin hydrochloride has been shown to be effective only in combination with an aminoglycoside for endocarditis due to enterococci (eg Enterococcus fecalis).
Vancomycin hydrochloride has been shown to be effective for the treatment of diphtheroid endocareditis. In early-onset prosthetic valve endocarditis caused by Staphylococcus epidermidis or diptheroids vancomycin hydrochloride has been administered successfully in combination with either rifampin an aminoglycoside or combined with both drugs.
Bacteriologic cultures of specimens should be obtained for isolation and identification of causative organisms and determination of susceptibilities to vancomycin hydrochloride.

Oral Therapy Vancomycin hydrochloride injection may be given orally for the treatment of antibiotic associated Pseudomembranous colitis due to Staphylococcus enterocolitis and Clostridium difficile.
Vancomycin hydrochloride is not effective orally when administered for other types of infection.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

**4.2 Posology and method of administration**
**Intravenous administration**
Solution concentrations of no more than 5 mg/ml are recommended. In selected patients in need of fluid restriction, solution concentration up to 10 mg/ml may be used; use of such higher concentrations may increase the risk of infusion-related events (see section 6.6).
Infusions should be given over at least 60 minutes. In adults, if doses exceeding 500 mg are used, a rate of infusion of no more than 10 mg/min is recommended. Infusion-related adverse events are related to both concentration and rate of administration of vancomycin.
The duration of treatment is guided by the severity of the infection and its clinical and bacteriological progression.
**Patients with normal renal and hepatic functions**
*Adults, adolescents and children over 12 years old:*
The recommended daily intravenous dose is 2000 mg (2g), divided into 500 mg doses administered every 6 hours or (1g) 1000mg every 12 hours. Each dose should be administered at no more than 10 mg/min or over a period of at least 60 minutes, whichever is longer.
For bacterial endocarditis, the generally accepted regimen is 1000 mg of 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.

*Children under 12 years old:*
The recommended intravenous dose is 10 mg/kg, every 6 hours. Each dose should be administered over a period of at least 60 minutes.

*Neonates and breast-feeding infants:*
The recommended initial dose is 15 mg/kg, followed by 10 mg/kg every 12 hours in the first week of life, and every 8 hours thereafter up to the age of one month. Each dose should be administered over at least 60 minutes. Close monitoring of serum concentrations of vancomycin is recommended. See section 'Patients with impaired renal function' below.

*Elderly patients:*
Lower maintenance doses than for adults may be required given decreased renal function in this group.

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

*Patients with impaired hepatic function:*
There is no evidence suggesting that dose should be reduced in patients with impaired hepatic function.

*Patients with impaired renal function:*
Dosage adjustment must be made in patients with impaired renal function. In order to optimize dosage, serum vancomycin concentrations should be measured by means of microbiological assay, radioimmunoassay, fluorescence polarization immunoassay, fluorescence immunoassay or high pressure liquid chromatography.

Calculation of vancomycin daily dose: measure creatinine clearance and use the table below (daily dose of vancomycin in mg is around 15 times the glomerular filtration rate in ml/min):

**VANCOMYCIN POSOLOGY**
**IN PATIENTS WITH IMPAIRED RENAL FUNCTION**

(Adapted from Moellering *et al*.)[1]

| **Creatinine clearance (ml/min)** | **Vancomycin dose (mg/24 hours)** |
|---|---|
| 100 | 1545 |
| 90 | 1390 |
| 80 | 1235 |
| 70 | 1080 |
| 60 | 925 |
| 50 | 770 |
| 40 | 620 |
| 30 | 465 |
| 20 | 310 |
| 10 | 155 |

1 Moellering RC, Krogstad DJ, Greenb1att DJ: Vancomycin therapy in patients with impaired renal function: a nomogram for dosage. Ann Intem Med 1981; 94:343.

This table is not valid for functionally anephric patients. For such patients, an initial dose of 15 mg/kg of body weight should be administered to achieve prompt therapeutic serum concentrations. The dose required to maintain stable concentrations is 1.9 mg/kg/24 hours.

When only serum creatinine is known, the following formula (based on sex, weight and age of patient) may be used to calculate approximate creatinine clearance, and actual creatinine clearance should be measured promptly. Calculated creatinine clearances (ml/min) are only estimates.

$$\text{Men} = \frac{\text{Weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine concentration (mg/100 ml)}}$$

Women = 0.85 x above value

The formula above should not be used in particular conditions with decreased renal function (shock, severe heart failure or oliguria), obesity, malnutrition, oedema or ascites, since it would give an overestimate of actual creatinine clearance.

Where possible, the creatinine clearance should always be determined.

In patients with slight or moderate renal impairment, the initial dose should not be lower than 15 mg/kg. In patients with severe renal impairment, it may be preferable to administer maintenance doses of 250 mg to 1 g once every several days rather than administering lower doses on a daily basis.

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.

**Oral administration**
**Treatment of colitis due to *C. difficile***
*Adults:* The usual daily dose is 0,5g to 2 g given in 4 divided doses (125 mg to 500 mg per dose) for 7 to 10 days.
*Children:* The usual daily dose is 40 mg/kg/day given in 4 divided doses, up to a maximum of 250 mg/dose, for 7 to 10 days.

*Method of administration:*
For intravenous infusion only, and not for intramuscular 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 500 mg/100ml or at least 1000mg/200 ml).
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.
The reconstituted solution may also be used for oral administration.
Therapeutic indications for intravenous and oral administration are different. Both administration routes could not be commuted.
For information about the preparation of the solution, please refer to section 6.6 special precautions for disposal and other handling.

**4.3 Contraindications**
**VancoAvenir** is contraindicated in patients with known hypersensitivity to vancomycin.

**4.4 Special warnings and precautions for use**

**Warnings:**
If severe acute hypersensitivity reactions occurs (e.g. anaphylaxis), 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).

Vancomycin hydrochloride is irritating to tissue and must be administered by intravenous route. Intramuscular injection or inadvertent extravasation causes pain and necrosis.

The safety and efficacy of vancomycin administration by the intrathecal route (intralumbar or intraventricular) have not been assessed.
Although the recommended route is intravenous, there have been reports of administration of vancomycin by the intraperitoneal route during continuous ambulatory peritoneal dialysis resulting in chemical peritonitis syndrome.
This can range from simple cloudy dialysate alone to cloudy dialysate with varying degrees of abdominal pain and fever. This syndrome usually clears quickly after discontinuation of intraperitoneal administration of vancomycin.

Rapid bolus administration (e.g., over several minutes) is associated with severe hypotension, shock and, rarely, cardiac arrest (see section 4.8 *Adverse reactions*) histamine like responses and maculopapular or erythematous rash ("red man's syndrome" or "red neck syndrome"). So vancomycin should be administered in a diluted solution (2.5 to 5.0g/l) at a rate not greater than 10 mg/min and over a period of not less than 60 minutes to avoid rapid infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions.

Thrombophlebitis may occur, the frequency and severity of which can be minimised by administering the drug slowly as a dilute solution (2.5 to 5 g/l), and by rotating the sites of infusion.

The frequency of infusion-related events (including hypotension, flushing, erythema, urticaria and pruritus) increases with the concomitant administration of anaesthetic agents. This can be minimised by the administration of vancomycin as a 60-minute infusion prior to anaesthetic induction.

Ototoxicity has been reported in patients receiving vancomycin. It may be transient or permanent (see section 4.8 *Adverse reaction*) in patients with prior hearing loss, or who have been given excessive intravenous doses, or who are receiving concomitant therapy with another ototoxic agent 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.
Clinically significant serum concentrations have been reported in some patients being treated for active *C. difficile*-induced pseudomembranous colitis after multiple oral doses of vancomycin. Therefore, monitoring of serum concentrations may be appropriate in these patients.

Nephrotoxicity: vancomycin should be used with caution in patients with impaired renal function since the possibility of toxic effects is far greater in the presence of high and prolonged blood concentrations. During treatment of these patients, or of patients receiving concomitant therapy with other nephrotoxic active substances (i.e. aminoglycosides), serial monitoring of renal function should be performed and particular care should be taken in following appropriate dosing schedules in order to minimise the risk of nephrotoxicity (see section 4.2 *Posology and method of administration*).

**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.
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.
All patients who receive vancomycin should be periodically examined for hematological and renal function parameters and also for auditory functions.
With prolonged duration of use, regular monitoring of vancomycin blood levels is indicated during therapy, particularly in patients with renal dysfunction or impaired hearing, or if ototoxic or nephrotoxic substances are co-administered, such as aminoglycosides. In such cases, renal function should be regularly monitored and the dosage adjusted to the reduction in renal function.
Regular monitoring of auditory function is required in patients with impaired auditory function, or if ototoxic medications are co-administered and in cases of renal dysfunction.

The administration of vancomycin by intraperitoneal injection during continuous ambulatory peritoneal dialysis has been associated with a syndrome of chemical peritonitis.

As with other broad-spectrum antibiotics, cases of pseudomembranous colitis have been reported. It is therefore important to bear this diagnosis in mind in patients who develop diarrhoea during or after antibiotic treatment. This type of colitis may be benign but can also be life-threatening. Broad-spectrum antibiotics shall be prescribed with caution to patients with a history of gastrointestinal illness, particularly colitis. Moderately severe cases generally cease on interruption of treatment. The appropriate measures shall be taken in other cases.

Medicinal products for injection must be inspected visually for particles and discolouration before use, provided that the solution or container permits such inspection (see section 6.6 *Instructions for use and handling*).

Following oral administration of repeat doses of vancomycin for the treatment of pseudomembranous colitis caused by *C. difficile*, clinically significant serum levels have been observed in some patients.

As with other antibiotics, prolonged use of vancomycin may result in the overgrowth of nonsusceptible microorganisms, principally fungi. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Reversible neutropenia has been reported (see section 4.8 *Adverse reactions*). Patients undergoing prolonged therapy with vancomycin or those who are receiving
concomitant drugs that may cause neutropenia should have periodic monitoring of the leukocyte count.

*Use in elderly patients:*
The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum levels. 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 nephrotoxic substances should be avoided.

*Use in breast-feeding infants/children:*
Serum vancomycin concentrations must be monitored in premature babies and neonates. The concomitant use of vancomycin and anaesthetic agents in children has been associated with erythema, histamine-like flushing in children and anaphylactoid reactions . If vancomycin has to be administered in surgical prophylaxis, it is recommended that the anaesthetic agents be

administered after the vancomycin infusion has been completed (see section 4.8 *Adverse reactions*).

**4.5 Interaction with other medicinal products and other forms of interaction**

Anaesthetics

The concomitant administration of intravenous vancomycin and anaesthetic agents such as nitrous oxide, halothane and fentanyl has been associated with erythema and anaphylactoid reactions relating to the release of histamine and other vasoactive amines. This can be minimised by the administration of vancomycin as a 60-minute infusion prior to anaesthetic induction (see section 4.8 *Adverse reactions*).

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.

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, lactation and Fertility**

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, colonization with yeast-like fungi and possibly sensibilisation). Considering the importance of this medicine for nursing mother, the decision to stop breastfeeding should be considered.

Fertility: No fertility (male or female) study is available for vancomycin.

**4.7 Effects on ability to drive and use machines**

There is no evidence that **VancoAvenir** affects the ability to drive or use machines.

**4.8 Adverse reactions**

The adverse reactions listed below are defined using the following MedDRA convention and system organ class database: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

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

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

| **System Organ Class** | **Frequency grouping** |
|---|---|
| Blood and lymphatic system disorders | Rare<br>- thrombocytopenia<br>- neutropenia,<br>- agranulocytosis,<br>- eosinophilia. |
| Immune system disorders | Rare<br>- anaphylactic reactions,<br>- hypersensitivity reactions. |
| Ear and labyrinth disorders | Uncommon<br>- transient or permanent loss of hearing.<br>Rare<br>- tinnitus,<br>- dizziness. |
| Cardiac disorders | Very Rare<br>- cardiac arrest. |
| Vascular disorders | Common<br>- decrease in blood pressure,<br>- thrombophlebitis.<br>Rare<br>- vasculitis. |
| Respiratory, thoracic and mediastinal disorders | Common<br>- dyspnoea,<br>- stridor. |
| Gastrointestinal disorders | Rare<br>- nausea<br>Very Rare<br>- pseudomembranous enterocolitis after intravenous administration. |
| Skin and subcutaneous tissue disorders | Common<br>- exanthema and mucosal inflammation,<br>- pruritus,<br>- urticaria.<br>Very Rare<br>- exfoliative dermatitis,<br>- Stevens-Johnson syndrome,<br>- Lyell's syndrome,<br>- IgA induced bullous dermatitis. |
| Renal and urinary disorders | Common<br>- renal insufficiency manifested primarily by increased serum creatinine or serum urea concentrations.<br>Rare<br>- interstitial nephritis,<br>- acute renal failure. |
| General disorders and administration site conditions | Common<br>- redness of the upper body and the face,<br>- pain and spasm of the chest and back muscles.<br>Rare<br>- drug fever, |

| | |
|---|---|
| | - shivering.<br>Very Rare<br>necrosis and pain at injection site |

During or shortly after rapid infusion anaphylactic reactions may occur, including hypotension, dyspnea, urticaria or pruritus. 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.
After oral administration, as vancomycin could be absorbed in case of digestive lesion, the risk of the above mentioned undesirable effects described cannot be eliminated.

**4.9 Overdosage**
*Signs and symptoms:* include nausea, vomiting, epigastric discomfort and diarrhoea.
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**
Pharmacotherapeutic group: other antibacterials; glycopeptides. ATC code: JO1XA01.

Action mechanism: the bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial cell membrane permeability and RNA synthesis.

Susceptibility
The following critical points of minimum inhibitory concentrations (MICs) enable sensitive microorganisms to be distinguished from resistant ones (NCCLS criteria).

| **Microorganism** | | | |
|---|---|---|---|
| Staphylococcus | S ≤ 4 mg/ml | I : 8-16 mg/ml | R ≥ 32 mg/ml |
| Enterococcus | S ≤ 4 mg/ml | I : 8-16 mg/ml | R ≥ 32 mg/ml |
| *Streptococci pneumoniae*, other streptococci | S ≤ 1 mg/ml | | |

The prevalence of acquired resistance may vary geographically and with time for given species, and local information on resistance should be consulted, particularly when treating severe infections. The information given below is solely an approximate guide on whether microorganisms are likely to be vancomycin-sensitive or not.

| **Susceptible** | % resistance |
|---|---|
| *Enterococcus faecalis** | 2 % |
| *Enterococcus faecium* | 8-24 % |
| *Listeria monocytogenes* | < 1 % |
| *Staphylococcus aureus** | < 1 % |
| Methicillin-resistant strains | < 1 % |
| Methicillin-sensitive strains | 0 % |
| *Staphylococcus epidermis* (including methicillin-resistant strains)* | 0 % |
| Coagulase negative staphylococci (including methicillin-resistant strains)* | < 1 % |
| *Streptococcus pneumoniae* including penicillin-resistant strains | 0 % |
| *Streptococcus pyogenes* | 0 % |
| *Streptococcus* viridans (viridans group)* | 4 % |
| *Clostridium dificile* | 0 % |
| *Clostridium species* | 0 % |

*The clinical efficacy for approved indications has been demonstrated on isolated sensitive strains

**Resistant**
*Enterococcus casseliflavus*
*Enterococcus gallinarum*
*Enterococcus flavescens*
Gram-negative bacilli
Mycobacteria
Leucosnostoc sp.
Pediococcus sp.
Lactobacilli (some species)
Fungi

Mechanism(s) of resistance
Resistance to vancomycin can be based on the following mechanisms:
- Change in target structure: This form of resistance has occurred over the past few years, particularly in the Enterococcus faecium species. This change is due to replacement of terminal D-alanine-D-alanine function of the amino acid side chain in a murein precursor with DAla-D-lactate, with the result that affinity to vancomycin is considerably reduced.
- In staphylococci, reduced susceptibility or resistance to vancomycin is based on overproduction of murein precursors, to which vancomycin is bound.

Cross-resistance: there is no cross-resistance between vancomycin and other antibiotics. Cross-resistance with teicoplanin has been reported.
Vancomycin-resistant enterococcus (VRE) is an increasing problem. Methicillin-resistant *Staphylococcus aureus* is also a growing problem, although there are only isolated cases presenting reduced susceptibility to vancomycin.

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.

**5.2 Pharmacokinetic properties**
*Absorption:*
Vancomycin is poorly absorbed p.o.
It is administered intravenously for the treatment of systemic infections. In patients with normal renal function, venoclysis of repeat doses of 1 g vancomycin (15 mg/kg) over 60 minutes produces mean plasma concentrations of around 63, 23 and 8 mg/1 immediately, 2 and 11 hours after completing the infusion, respectively. Venoclysis of repeat doses of 500 mg over 30 minutes produces mean plasma concentrations of around 49, 19 and 10 mg/l immediately, 2 and 6 hours after completing the infusion, respectively. The plasma levels obtained after repeat doses are similar to those obtained after a single dose.

*Distribution:*
At vancomycin serum concentrations of 10 to 100 mg/1, approximately 55% of the drug binds to plasma proteins, as measured by ultrafiltration.
After intravenous administration of vancomycin hydrochloride, inhibitory concentrations are found in pleural, pericardial, ascetic and synovial fluids, cardiac muscle and in heart valves, in urine, in peritoneal dialysis fluid and in the atrial auricle tissue.
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 noninflamed 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.
After oral repeated administrations of vancomycin, vancomycin plasmatic oncentrations have been observed in patients treated for pseudomembranous colitis due to Clostridium difficile.

*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 7.5days). 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**
**Carcinogenesis, mutagenicity and effects on fertility**:
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**
Contains no excipients.

**6.2 Incompatibilities**
Vancomycin solutions are acid, and must remain so to prevent precipitates from forming. They must therefore not be mixed with alkaline solutions.
It has been demonstrated that vancomycin solutions and beta-lactam antibiotic solutions are physically incompatible. The likelihood of precipitates forming increases with higher concentrations of vancomycin.
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 6.3
Intravenous routes should be washed carefully between administrations of these antibiotics. It is also recommended that vancomycin solutions be diluted to a concentration of 5 mg/ml or lower.

Although intravitreous injection is not an authorised administration route for vancomycin, there have been reports of the formation of precipitates after intravitreous injection of vancomycin and ceftadizime for the treatment of endophthalmitis using different syringes and needles. The precipitates dissolved gradually with complete clearance of the vitreous cavity over two months and improved visual acuity.

**6.3 Shelf life**
Prior to reconstitution: 2 years.

After reconstitution:

Chemical and physical stability for use has been demonstrated for 14 days at 2°C-8°C and for 8 hours at below $25^0$C if the solvent is 5% dextrose or 0.9% sodium chloride.

From the microbiological point of view, the product should be administered immediately. If this is not the case, times and conditions of storage for use before administration shall be no more than 24 hours at 2°C - 8ºC unless reconstitution and dilution have been carried out in controlled and validated aseptic conditions.

**6.4 Special precautions for storage**
Protect from light.
Before reconstitution: do not store above 25 °C.
After reconstitution: store between 2 °C and 8 ºC (in the fridge).

**6.5 Nature and contents of container**
Type II glass vial with rubber stopper sealed with aluminium cap.

**6.6 Instructions for use and handling**
For intravenous administration

**VancoAvenir** 500 mg, powder for solution for injection:

1. Reconstitution: at moment of use, add 10 ml water for injection to the vial containing 500 mg vancomycin; in this way a concentration of 50 mg/ml is obtained.
2. Dilution: immediately following reconstitution, dilute the reconstituted solution by adding 100 ml solvent.

The required dose diluted in this manner can be administered intravenously over a period of not less than 60 minutes.

**VancoAvenir** 1 g, powder for solution for injection:

1. Reconstitution: at moment of use, add 20 ml water for injection to the vial containing 1 g vancomycin; in this way a concentration of 50 mg/ml is obtained.
2. Dilution: immediately following reconstitution, dilute the reconstituted solution by adding 200 ml solvent.

The required dose diluted in this manner can be administered intravenously over a period of not less than 60 minutes.

For oral administration
Intravenous vancomycin hydrochloride can be administered orally for antibiotic-related pseudomembranous colitis caused by *C. difficile* and for treatment of staphylococcal enterocolitis. It is not effective p.o. for other types of infection. The normal total daily dose for adults is 500 mg to 2 g given in 3 or 4 divided doses for a period of 7 to 10 days. The normal total daily dose for children is 40 mg/kg body weight given in 3 or 4 divided doses over a period of 7 to 10 days. The total daily dose must not exceed 2 g. The appropriate dose can be diluted in 30 ml water and given to the patient to drink. Common flavouring syrups may be added to the solution to make it more palatable. The diluted solution may be administered via a nasogastric tube.

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. PRODUCTS' REGISTRATION NUMBERS**
**VancoAvenir 500 mg** - 153-17-34018-00
**VancoAvenir 1 g** - 153-18-34020-00

**8. MANUFACTURER**
Laboratorio RAMÓN SALA, S.L
C/ Gran Capità, 10
08970 Sant Joan Despí
Barcelona

**9. LICENSE HOLDER AND IMPORTER**
BioAvenir Ltd.
1 David Hamelech St.
Herzelia Pituach, 4666101

**The format of this leaflet has been determined by the Ministry of Health and the content thereof has been checked and approved in December 2014**

Vanco-500mg&1g, 12/2014-1