SUMMARY OF PRODUCT CHARACTERISTICS

VOXIN®

1.NAME OF THE MEDICINAL PRODUCT

VOXIN®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains Vancomycin hydrochloride equivalent to 500 mg Vancomycin.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

A. Vancomycin hydrochloride administered by intravenous infusion is indicated in the treatment of the following infections:
Staphylococcal infections: Vancomycin is indicated for the treatment of severe or life-threatening infections caused by susceptible strains of methicillin-resistant staphylococci.

It is indicated for penicillin-allergic patients, for patients who cannot receive other medicines or who have failed to respond to those and for infections caused by vancomycin-susceptible micro-organisms that are resistant to other antibiotics. Vancomycin hydrochloride is indicated for initial treatment when methicillin-resistant staphylococci are suspected, but after susceptibility test results are available, treatment should be adjusted accordingly.

Endocarditis: Vancomycin is effective in the treatment of staphylococcal endocarditis. Vancomycin is effective alone or in combination with an aminoglycoside in endocarditis caused by *Streptococcus viridans* or *Streptococcus bovis* and in endocarditis caused by enterococci (e.g. *E. faecalis*), always in combination with gentamycin. Vancomycin is also effective in the treatment of diphtheroid endocarditis. Vancomycin has been used successfully in combination either with rifampicin or some aminoglycoside or both in early-onset prosthetic valve endocarditis caused by *S. aureus, S. epidermidis* or diphtheroids.

The intravenous administration of vancomycin alone or in combination with gentamycin, has been recommended as prophylaxis against bacterial endocarditis in penicillin-allergic patients, who have congenital heart disease or rheumatic or other acquired valvular heart disease, when these patients undergo dental procedures or surgical procedures which require chemopropylaxis.

Other infections: Vancomycin effectiveness has been documented in many infections due to staphylococci, including septicemia, osteomyelitis, lower respiratory tract infections, and skin and soft-tissue infections. When staphylococcal infections are localized and purulent, antibiotics are used as adjuvants to appropriate surgical measures.

B. Oral administration of vancomycin hydrochloride is indicated in the treatment of antibiotic-associated severe pseudomembranous colitis caused by *Clostridium difficille* and for staphylococcal enterocolitis. ***Vancomycin hydrochloride is not effective orally for other types of infections.***

Specimens for microbiologic cultures should be obtained in order to isolate and identify the pathogenic micro-organism that causes the infection and to determine its susceptibility to vancomycin. Treatment may be initiated while waiting the results of these tests. Anti-bacterial treatment is adjusted according to the results.

4.2 Dosage and route of administration
The recommended route of administration of vancomycin is the intravenous infusion.

Adverse events due to infusion are related to both concentration and rate of administration of vancomycin. In general, vancomycin should be administered in solution of up to 5 mg/ml concentration and with a rate of administration 10 mg/min or lower (see section 4.4. Precautions). In some patients when fluid restriction is needed, a concentration up to 10mg/ml may be administered, however, caution is required because higher concentrations increase the risk of infusion-related events. However, infusion-related events may occur at any concentration and/or rate of administration of vancomycin.

Intravenous infusion:

Adults: The recommended adult intravenous dosage is 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours. Each dose should be administered at rate no higher than 10mg/min or over a period of at least 60 minutes for prolonged administration. In meningitis, the total daily dose can reach up to 4g.

Other patient factors, such as age or obesity, may require for modification of the usual intravenous daily dose.

Children: The usual daily dosage of vancomycin in children is 10 mg/kg body weight given every 6 hours. Each dose should be administered over a period of at least 60 minutes. The total intravenous daily dosage of vancomycin in children is 40 mg/kg body weight and can be divided and added to the solutions administrated to the children to cover the 24 hour needs.

Infants and Neonates: An initial dosage of 15 mg/kg is recommended followed by 10 mg/kg every 12 hours for the first week of life and every 8 hours thereafter up to the age of 1 month.

Close monitoring of serum concentration of vancomycin may be warranted in these patients.

Oral administration:

The oral administration of vancomycin is indicated only in the treatment of antibiotic-associated pseudomembranous colitis caused by *Clostridium difficille* and of staphylococcal enterocolitis. The usual total dosage in adults is 500 mg to 2 g given in 3 or 4 doses for 7 to 10 days and the usual total dosage in children is 40mg/kg of body weight in 3 or 4 doses for 7 to 10 days. The total daily dosage should not exceed 2 g.
The appropriate dosage may be diluted in 1 glass of water and given to the patient to drink it. Common flavouring syrups may be added to the solution to improve the taste for oral

administration. The diluted solution may be administered via a nasogastric tube. *Vancomycin hydrochloride is not effective orally for other types of infections.*

Patients with renal impairment and elderly patients: In patients with renal impairment a decreased dosage should be administered. Also, in premature infants and in elderly, greater dosage reduction than recommended may be necessary because of decreased renal function. Measurements of vancomycin serum concentration may contribute in optimal treatment, especially in seriously ill patients with renal impairments.

Vancomycin serum concentration can be determined by use of microbiology assay, fluorescence immunoassay or high-pressure liquid chromatography.

In case where creatinine clearance is provided in patients with renal impairment, it is recommended to follow the dosage scheme below: (The daily dosage of vancomycin hydrochloride (mg) is about 15 times the glomerular filtration rate (ml/min).

DOSAGE TABLE
IN PATIENTS WITH RENAL IMPAIRMENT

Creatine Clearance ml/min	**Vancomycin dosage (mg/24h)**
100	1545
90	1390
80	1235
70	1080
60	925
50	770
40	620
30	465
20	310
10	155
The initial dose should be no less than 15mg/kg, even in patients with mild to moderate renal failure.	

In anephric patients, an initial dose of 15 mg/kg of body weight should be given to achieve promptly therapeutic serum concentrations. The dose required to maintain steady concentrations is 1,9 mg/kg/24h. In patients with terminal stage of renal impairment it may be more practical to administer maintenance single dosages of 250 to 1000 mg per several days' intervals rather than administering the drug on a daily basis.

In anuria, it is recommended a dose of 1000 mg every 7 days.

NOTE: When the serum creatinine concentration is known, the following formula (based on sex, weight, and age of the patient) may be used to calculate creatinine clearance. The serum creatinine should represent a steady state of renal function.

Men: $\frac{\text{Weight (kg) x (140 – age (in years))}}{\text{72 x serum creatinine (mg/dl)}}$

Women: 0,85 x the above value

If the serum creatinine does not represent a steady state of renal function, then the estimated value for creatinine clearance is not valid. Thereby, such a calculated clearance can provide higher values in patients with the following conditions:

1) associated with decreased renal function, such as shock, severe heart failure or oliguria,
2) where there is a disorder of the normal relationship between muscle mass and body weight such as in obese patients or these with liver disease, oedema, or ascites and
3) associated with debilitation, malnutrition or inactivity.

The safety and efficacy of the intrathecal administration of vancomycin s have not been documented.

4.3 Contraindications

Vancomycin is contraindicated in patients with known hypersensitivity to this antibiotic.

4.4 Special warning and special precautions during use

Warnings

Rapid bolus administration (e.g. over some minutes) may cause hypotension and collapse. Vancomycin should be administered in a dilute solution over a period of not less than 60 minutes to avoid rapid-infusion-related reactions. Discontinuation of the infusion, usually results in prompt resolution of these reactions.

Ototoxicity has been reported in patients who received excessive doses or had already an underlying hearing loss or who received concomitant treatment with another ototoxic agent (e.g. aminoglycoside).

Vancomycin should be used with caution in patients with renal failure, due to high, prolonged blood concentrations. Dosage of vancomycin hydrochloride must be adjusted in these patients (see section 4.2 Dosage and Route of Administration).

In order to minimize the risk of nephrotoxicity when treating patients with underlying renal impairment or patients receiving concomitantly treatment with an aminoglycoside, continuous control of renal function should be performed and special care should be taken in following appropriate dosing schedules (see section 4.2 Dosage and Route of Administration).

Pseudomembranous colitis has been reported with all broad spectrum antibiotics (including macrolides, semi-synthetic penicillins and cephalosporins). This diagnosis should be considered in patients who develop diarrhea after the use of antibiotics. The severity ranges from mild to life-threatening. Mild cases of pseudomembranous colitis simply respond to drug discontinuation. Appropriate measures should be taken in moderate or severe cases.

In cases of long-term use of antibiotics, it should be considered the possibility of occurring of resistant micro-organisms resulting in their overgrowth. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Precautions

Reversible neutropenia has been reported in patients receiving vancomycin hydrochloride (see section 4.8 Adverse Reactions). Patients who will undergo prolonged treatment should have periodic tests of the leukocyte count.
Patients who are receiving concomitantly drugs that may cause neutropenia should be tested periodically for the count of leukocytes.

Vancomycin hydrochloride should be administered **intravenously**. Pain, tenderness and probably injection site necrosis occur with intramuscular injection of Vancomycin hydrochloride or with inadvertent extravagation. Thrombophlebitis may occur, the frequency and severity of which can be minimized by administering the drug slowly as a diluted solution (2,5 to 5g/l) and by alternation of the injection sites.

There have been reports that the frequency of infusion-related events (including hypotension, flushing, erythema, urticaria and pruritus) increases with the concomitant administration of anesthetic drugs. Infusion-related events may be minimized by the administration of vancomycin as a 60-minute infusion prior to anesthesia induction.

The safety and efficacy of vancomycin administration by the intrathecal (intvalumbar or intraventricular) routes have not been documented.

It has been reported that the intraperitoneal administration of vancomycin hydrochloride during continuous portable peritoneum clearance resulted in a *syndrome of chemical peritonitis*. This syndrome resolves soon with the discontinuation of the intraperitoneal administration of vancomycin.

Children: In premature neonates and young infants, it may be appropriate to confirm the desired vancomycin serum concentrations. Concomitant administration of vancomycin and anesthetic drugs have been associated with erythema and histamine-like flushing in children (see section 4.8 Adverse Reactions).

Elderly: The recommended dosage of vancomycin should be adjusted in the elderly because of the decreased renal function (see section 4.2. Dosage and Route of Administration).

4.5 Drug interactions and other forms of interactions

Concomitant administration of vancomycin and anesthetic drugs has been associated with erythema and histamine like flushing and anaphylactoid reactions (see section 4.4 Precautions and 4.8 Adverse Reactions).

Concomitant as well as sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymixin B, colistin, viomycin, cisplatin, requires careful observation.

4.6 Pregnancy and lactation

In a clinical study where the drug was administered intravenously in pregnant mothers for the treatment of serious staphylococcal infections, no neurosensory hearing loss or nephrotoxicity related to vancomycin was observed in the foetus. Vancomycin hydrochloride was found in umbilical cord blood. The number of the patients in this study was limited and vancomycin hydrochloride had been administered only in the second and third trimester of pregnancy. It is

not known whether vancomycin can cause fetal injury when given during pregnancy or to affect the reproductive capacity.

Since animal reproduction studies are not always indicative of the reactions to human, vancomycin should be administered to a pregnant woman only if absolutely needed.

It is not known whether the drug is excreted in human milk. Caution should be exercised when vancomycin is administered to a nursing woman. Since adverse events may occur in the nursing infant, it should be decided either to interrupt lactation or drug administration, taking under consideration of the necessity of drug administration to the mother.

4.7 Effect on the ability to drive and use machinery

It is unlikely that vancomycin affects the ability to drive of the patients.

4.8 Adverse reactions

Infusion - related events: With rapid infusion of vancomycin hydrochloride, patients may develop anaphylactoid reactions, which include hypotension, dyspnea with wheezing, urticaria or pruritus. Also erythema in the neck, pain and muscle spasm in the chest and back. These reactions usually resolve within 20 minutes but may persist for hours. Such events are rare if vancomycin hydrochloride is given slowly over 60 minutes infusion.
Slow infusion (rate 10mg/min or slower) of vancomycin hydrochloride greatly reduces the possibility of anaphylactoid events.

Nephrotoxicity: Renal failure, which is mainly developed by increased serum creatinine or blood urea nitrogen concentrations especially in patients who received high dosages of vancomycin hydrochloride has been reported rarely. Rare cases of interstitial nephritis in patients receiving concomitantly aminoglycosides or with preexisting renal disorder. Azotemia resolved when vancomycin hydrochloride was discontinued.

Gastrointestinal System: Pseudomembranous colitis may occur during or after treatment with antibiotics (see section 4.4. Warnings).

Ototoxicity: Hearing loss associated with vancomycin hydrochloride has been reported in some tens of cases, mostly in patients with renal disorder or preexisting hearing loss or in patients who were receiving concomitant treatment with an ototoxic drug. Vertigo, dizziness, and tinnitus have been reported rarely.

Blood and laboratory results: Reversible neutropenia, starting about one week or more after onset of treatment with vancomycin hydrochloride or after a total dosage of more than 25g has been reported. Neutropenia is promptly reversible when vancomycin is discontinued. Thrombocytopenia has been reported rarely. Reversible agranulocytosis has been reported rarely, although the causative correlation has not been established.

Thrombophlebitis: Inflammation at the injection site has been reported.

Miscellaneous: Anaphylaxis, drug fever, chills, nausea, eosinophilia, rashes (exfoliative dermatitis), bullous dermatopathia (with linear deposition of IgA), vasculitis, Stevens-Johnson syndrome, toxic epidermal necrolysis have been reported rarely with administration

of vancomycin. Chemical peritonitis has been reported following the intraperitoneal administration of vancomycin (see section 4.4. Warnings).

4.9 Overdosage symptoms, Measures of Management and Antidotes

Supportive treatment is recommended, with maintenance of glomerular filtration. Vancomycin is poorly elininated by hemodialysis. Hemoperfusion with resin Amberlite XAD-4 has been reported to offer limited benefit. The beneficial result of pharmaceutical diuresis and hemodialysis in cases of overdosage with vancomycin has not been determined. In managing overdosage, it should be considered the possibilities of multiple pharmaceutical overdosages, drug interactions and unusual pharmacokinetic in the particular patient.

5. PHARMACOLOGICAL PROPERTIES

ATC code: J01XA01

5.1 Pharmacodynamic Properties

Vancomycin is a purified by chromatography, tricyclic glycopeptide antibiotic. It is administered intravenously for the treatment of systemic infections. Intramuscular administration is painful.
The bactericidal action of vancomycin results from the inhibition of the bacterial cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis. There is no cross-resistance between vancomycin and other antibiotics.
Vancomycin has been demonstrated to be active against streptococci and staphylococci and the following microorganisms:
Stapylococcus aureus (including methicillin-resistant strains)
Stapylococcus epidermidis (including methicillin-resistant strains)
Streptococcus pyogenes, *Streptococcus pneumoniae*, (including penicillin-resistant strains), *Streptococcus agalactiae*, *Streptococcus bovis*, *Viridans streptococci*, *Enterococci*, *Clostridium difficile* and *Diphtheroids*.

Other micro-organisms that are susceptible to vancomycin *in vitro* are the following: *Listeria monocytogenes*, *Lactobacillus spp*, *Actinomyces spp*, *Clostridium spp* and *Bacillus spp*.

Vancomycin is not active *in vitro* against gram-negative bacilli, mycobacteria or fungi.

The combination of vancomycin with aminoglycoside acts synergistically *in vitro* against many strains of *S. aureus*, non-enterococcal group D streptococci, enterococci and *Streptococcus spp*. (viridans group).

Susceptibility Test – Infusion Assays

Susceptibility to vancomycin is determined by quantitative methods which count the zones diameter. This procedure is defined by the National Committee for Clinical Laboratory Standards (NCCLS) organization. The result is based on the correlation of the diameters achieved in the disk test with the minimum inhibition concentrations (MIC) for vancomycin. The results of standard single-disk susceptibility test with a disk containing 30µg vancomycin hydrochloride should be interpreted according to the following criteria.

According to National Committee for Clinical Laboratory Standards (NCCLS) instructions, strains of *Staphylococcus spp* with a zone diameter >15mm are considered susceptible, when tested with the method of susceptible disk. All strains with a zone diameter 14mm or less should be tested with the method of subsequent dilutions. All strains that are assessed as resistant with the method of subsequent dilutions should be forwarded to a reference laboratory.

According to NCCLS, the limits of the method of susceptible disks for the strains of *Enterococcus spp* are determined as follows:

Zone diameter (mm)	Interpretation
≥17	Susceptible
15-16	Intermediate susceptibility
<14	Resistant

Standardized procedures require the use of laboratory control organisms. The 30μg vancomycin disk should give the following zone diameters:

Organism	Zone diameter (mm)
S. aureus ATCC 25923	15-19

Using a standardized method of subsequent dilutions, a bacterial isolate [according to CLSI organization] may be considered susceptible if the MIC value for vancomycin is ≤ 2μg/ml. Micro-organisms are considered resistant to vancomycin if the MIC is ≥16μg/ml. If MIC value is less than 8μg/ml but greater than 4μg/ml are considered to be of intermediate susceptibility. However, it must be pointed out that treatment with vancomycin is possible to fail if the MIC value of *S. aureus* strain is >0.5μg/ml.

As with the standard dilution methods, subsequent dilutions procedures require the use of laboratory control micro-organisms. Standard vancomycin powder should give MIC values in the range of 0,5 to 2,0mg/l for *S. aureus* ATCC 29213. For *Enterococcus faecalis* ATCC 29212, the MIC values should be ranged between 1,0 and 4,0mg/l.

Strains of *S. aureus* with decreased susceptibility to glycopeptides have been isolated in Japan, USA, Europe and Far East and they are named after the initial VISA (Vancomycin-intermediate Staphylococcus aureus) or GISA (Glycopeptide-intermediate Staphylococcus aureus). Most of the strains seem to be developed in the ground of infections due to methicillin resistant *Staphylococcus aureus* strains (MRSA) in patients who were in long-term treatment with vancomycin and have correlated with cases of vancomycin failure.

Their identification in laboratory is difficult and the disk method is not reliable. The American Centre of Control and Disease Prevention (CDC) has instituted the following criteria for the recognition and identification of GISA strains, which are analyzed in the table.

Technique	Result	Comments
Broth microdilution	MIC of vancomycin	Maintenance of the test for

	8-16μg/ml in Mueller-Hinton broth	24 hours
Brain heart infusion agar with addition of vancomycin 6μg/ml	Growth ≥1 colony after 24 hours	*S. aureus* ATCC 25923 strain is used as negative control and *Enterococcus faecalis* ATCC 51299 as positive control.
Etest	MIC of vancomycin ≥6μg/ml in Mueller-Hinton broth	Maintenance of the test for 24 hours

Note: In order to define a strain as VISA or GISA, ALL THE THREE CRITERIA must be fulfilled.

According to CDC recommendations the surveillance of *Staphylococcus aureus* strains for the development of intermediate resistance to glycopeptides should be focused on strains with MIC ≥4μg/ml and on MRSA strains isolated from patients at increased risk developing GISA (e.g. hemodialysed patients in portal peritoneal dialysis and/or in long-term treatment with glycopeptides, patients with infections caused by *Staphylococcus spp* on foreign bodies, e.t.c.).

Use of vancomycin in micro-organisms considered intermediate susceptible requires detailed determination of MIC for all anti-staphylococcal antibiotics and simultaneous counsel by a specialist.

5.2 Pharmacokinetic properties

Vancomycin is poorly absorbed after oral administration. In subjects with normal renal function, multiple intravenous doses of 1g of vancomycin (15mg/kg) infused over 60 minutes, achieve mean plasma concentrations approximately 63mg/l (immediately after the infusion), approximately 23mg/l (two hours after infusion) and approximately 8mg/l (eleven hours after the end of the infusion). Multiple doses of 500 mg infused over 30 minutes, achieve mean plasma concentrations approximately 49mg/l (immediately after the infusion), approximately 19mg/l (two hours after infusion) and approximately 10mg/l (six hours after the infusion). The plasma concentrations after multiple doses are similar to those after a single dose.

The mean plasma half-life of vancomycin is 4 to 6 hours in subjects with normal renal function. Within the first 24 hours about 75% of the administered dose of vancomycin is excreted in urine by glomerular filtration. Mean plasma clearance is about 0,058 l/kg/h, and mean renal clearance is about 0,048 l/kg/h. Renal impairment slows down the excretion of vancomycin. In anephric patients, the average elimination half-life is 7,5 days. The distribution coefficient ranges from 0,3 to 0,43 l/kg. There is no apparent metabolism of the drug. About 60% of an intraperitoneal dose of vancomycin administered during peritoneal dialysis is absorbed systematically in 6 hours. Serum concentrations about 10mg/l are achieved by intraperitoneal injection of 30mg/kg of vancomycin.
Total systemic and renal clearance of vancomycin may be reduced in elderly.

Vancomycin is approximately 55% serum protein bound as measured by ultrafiltration at vancomycin serum concentrations 10mg/l to 100mg/l. After intravenous administration of vancomycin hydrochloride, inhibitory concentrations are found in pleural, pericardial, ascetic and synovial fluid, in urine, in peritoneal dialysis fluid and in atrial appendage tissue.

Vancomycin hydrochloride does not readily diffuse into the cerebrospinal fluid, but when the meninges are inflamed, penetration into the spinal fluid occurs.

Although vancomycin is not effectively eliminated by either hemodialysis or peritoneal dialysis, there have been reported cases of increase of vancomycin clearance by hemodiffusion and hemofiltration.

5.3 Preclinical safety data

The mean lethal intravenous dose is 312 mg/kg in rats and 400 mg/kg in mice.
It is not known whether vancomycin affects reproduction capacity. In a clinical study, vancomycin was administered to pregnant women in the 3^{o} trimester for the treatment of severe staphylococcal infections. No ototoxicity or nephrotoxicity attributable to vancomycin was observed, although vancomycin was detected in umbilical cord blood. Since the number of women treated in this study was small and vancomycin administration was limited, the results of use of vancomycin in pregnancy are not known.
No studies have been conducted in animals to evaluate the possibility of causing cancer or mutations following the administration of vancomycin.

6. PHARMACEUTICAL PARTICULARS

6.1 Qualitative composition of excipients

20% Solution hydrochloric acid

6.2 Incompatibilities

After reconstitution, vancomycin solution has a low pH which may cause chemical or physical incompatibility on its mix with other substances. Mixing with alkaline solutions should be avoided.
Natural incompatibility has been observed when vancomycin solutions were mixed with β-lactamic antibiotics. The possibility of precipitation increases in solutions with high vancomycin concentrations. It is recommended adequate wash out of the intravenous lines with saline in between the administration of these antibiotics and vancomycin administration should be in dilute solution (concentration up to 5mg/ml).
Although intravitreous injection is not an approved administration route for vancomycin, precipitation has been observed after intravitreous injection of vancomycin and ceftazidime, when administered successively at one hour interval for the treatment of endophalmitis, although administered in separate syringes and needles. Gradual dissolution of the precipitation and complete clearance of the vitreous body were reported within two months with significant improvement of the visual acuteness.

6.3 Shelf life

Before reconstitution: 24 months below 25^{o}C
After reconstitution with sterile water for injection: 96 hours when stored in a refrigerator (2-8^{o}C).
Following further dilution, see section 6.6 Instructions for use

6.4 Special precautions for storage

See section 6.3 Shelf life and section 6.6 Instructions for use

6.5 Nature and contents of container

Carton containing one vial. Each vial contains 500mg of sterile whitish lyophilized powder of vancomycin.

6.6 Instructions for use

The reconstitution of the lyophilized powder for injection is done immediately before use by adding 10ml of sterile water for injection. After reconstitution, vial provides a solution of 50mg/ml. **FURTHER DILUTION IS REQUIRED.**

Reconstituted solution containing 500mg of vancomycin must be further diluted with at least 100ml of diluent. The desired dose of the diluted, by this manner, antibiotic on concentration 2,5g/l to 5,0g/l, should be administered intermittently by intravenous infusion over a period of at least 60 minutes.

Compatibility with other drugs and intravenous solutions:

From chemical point of view, solutions which are obtained after the dilution with 5% Dextrose solution or 0,9% Sodium Chloride or Ringer's solution may be stored in refrigerator (2-8^{o}C) for 14 days without a significant loss of their titer.

Solutions which are obtained after dilution with the following fluids may be stored in refrigerator (2-8^{o}C) for 96 hours:
5% Dextrose Injection & 0,9% Sodium Chloride Injection U.S.P.
Lactated Ringer's Injection U.S.P.
Lactated Ringer's Injection U.S.P. & 5% Dextrose Injection
Normosol® M & 5% Dextrose
Isolyte® E
Acetated Ringer's Injection

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

Vancomycin solution has a low pH and may cause a natural instability of other compounts.

Pharmaceutical products which are intended for parenteral administration should be inspected visually prior to administration for particulate matter and discolouration whenever diluent and container permit.

6.7 Name and address of responsible of Marketing Authorization

VIANEX S.A., Tatoiou str., 146 71 Nea Erythrea, Tel. 210 8009111-120, Fax : 210 8071573

7. MARKETING AUTHORIZATION NUMBER

8. DATE OF FIRST MARKETING AUTHORIZATION

9. DATE OF REVISION OF THE PRESENT TEXT

16-6-2009

VOXIN® is only for hospital use