

VANCOMYCIN HYDROCHLORIDE - vancomycin hydrochloride injection
Xellia Pharmaceuticals ApS

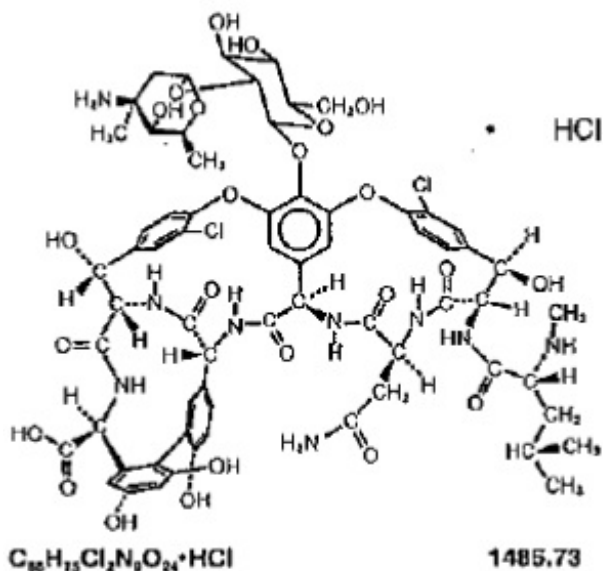
Vancomycin Hydrochloride for Injection, USP
PHARMACY BULK PACKAGE – NOT FOR DIRECT INFUSION
Rx Only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of vancomycin hydrochloride for injection, USP and other antibacterial drugs, vancomycin hydrochloride for injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Vancomycin hydrochloride for injection, USP is a lyophilized powder, for preparing intravenous (IV) infusions, in Pharmacy Bulk Package bottles containing the equivalent of 5 g or 10 g vancomycin base. 500 mg of the base are equivalent to 0.34 mmol. When reconstituted with Sterile Water for Injection to a concentration of 50 mg/mL for the 5 g Pharmacy Bulk Package bottle and 100 mg/mL for the 10 g Pharmacy Bulk Package bottle, the pH of the solution is between 2.5 and 4.5. Vancomycin hydrochloride for injection, USP should be administered intravenously in diluted solution (see DOSAGE AND ADMINISTRATION).

Vancomycin is a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*). The chemical name for vancomycin hydrochloride is 3S-[3R*,6S*(S*),7S*,22S*,23R*,26R*,36S*,38aS*]-3-(2-Amino-2-oxoethyl)-44-[[2-O-(3-amino-2,3,6-trideoxy-3-C-methyl- α -L-lyxo-hexopyranosyl)- β -D-glucopyranosyl]oxy]-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[[4-methyl-2-(methylamino)-1-oxopentyl]amino]-2,5,24,38,39-pentaoxo-22H-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1H,16H-[1,6,9]oxadiazacyclohexadecino[4,5-m][10,2,16]-benzoxadiazacyclotetracosine-26-carboxylic acid, monohydrochloride. The molecular formula is $C_{66}H_{75}Cl_2N_9O_{24} \cdot HCl$ and the molecular weight is 1,485.74. Vancomycin hydrochloride has the following structural formula:



A pharmacy bulk package is a sterile dosage form containing many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for IV infusion. AFTER RECONSTITUTION FURTHER DILUTION IS REQUIRED BEFORE USE.

CLINICAL PHARMACOLOGY

Vancomycin is poorly absorbed after oral administration.

In subjects with normal kidney function, multiple intravenous dosing of 1 g of vancomycin (15 mg/kg) infused over 60 minutes produces mean plasma concentrations of approximately 63 mcg/mL immediately after the completion of infusion, mean plasma concentrations of approximately 23 mcg/mL 2 hours after infusion, and mean plasma concentrations of approximately 8 mcg/mL 11 hours after the end of the infusion. Multiple dosing of 500 mg infused over 30 minutes produces mean plasma concentrations of about 49 mcg/mL at the completion of infusion, mean plasma concentrations of about 19 mcg/mL 2 hours after infusion, and mean plasma concentrations of about 10 mcg/mL 6 hours after infusion. The plasma concentrations during multiple dosing are similar to those after a single dose.

The mean elimination half-life of vancomycin from plasma is 4 to 6 hours in subjects with normal renal function. In the first 24 hours, about 75% of an 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 dysfunction slows excretion of vancomycin. In anephric patients, the average half-life of elimination is 7.5 days. The distribution coefficient is 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 systemically in 6 hours. Serum concentrations of about 10 mcg/mL are achieved by intraperitoneal injection of 30 mg/kg of vancomycin. However, the safety and efficacy of the intraperitoneal use of vancomycin has not been established in adequate and well-controlled trials (see PRECAUTIONS).

Total systemic and renal clearance of vancomycin may be reduced in the elderly. Vancomycin is approximately 55% serum protein bound as measured by ultrafiltration at vancomycin serum concentrations of 10 to 100 mcg/mL. After IV administration of vancomycin, inhibitory concentrations are present in pleural, pericardial, ascitic, and synovial fluids; in urine; in peritoneal dialysis fluid; and in atrial appendage tissue. Vancomycin does not readily diffuse across normal meninges into the spinal fluid; but, when the meninges are inflamed, penetration into the spinal fluid occurs.

MICROBIOLOGY

The bactericidal action of vancomycin results primarily from inhibition of 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 is not active *in vitro* against gram-negative bacilli, mycobacteria, or fungi.

Synergy

The combination of vancomycin and an aminoglycoside acts synergistically *in vitro* against many strains of *Staphylococcus aureus*, *Streptococcus bovis*, enterococci, and the viridans group streptococci.

Vancomycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic gram-positive microorganisms

Diphtheroids

Enterococci (e.g., *Enterococcus faecalis*)

Staphylococci, including *Staphylococcus aureus* and *Staphylococcus epidermidis*

(including heterogeneous methicillin-resistant strains)

Streptococcus bovis

Viridans group streptococci

The following *in vitro* data are available, **but their clinical significance is unknown.**

Vancomycin exhibits *in vitro* MIC's of 1 mcg/mL or less against most ($\geq 90\%$) strains of streptococci listed below and MIC's of 4 mcg/mL or less against most ($\geq 90\%$) strains of other listed microorganisms; however, the safety and effectiveness of vancomycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

Listeria monocytogenes

Streptococcus pyogenes

Streptococcus pneumoniae (including penicillin-resistant strains)

Streptococcus agalactiae

Anaerobic gram-positive microorganisms

Actinomyces species

Lactobacillus species

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution method ^{1,2} (broth, agar or microdilution) or equivalent using standardized inoculum and concentrations of vancomycin powder. The MIC values should be interpreted according to the criteria in Table 1.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure ^{2,3} requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg of vancomycin to test the susceptibility of microorganisms to vancomycin. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for vancomycin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 mcg vancomycin disk should be interpreted according to the following criteria in Table 1.

Table 1: Susceptibility Test Interpretive Criteria for Vancomycin

Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion Diameters (mm)
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Pathogen	Susceptible (S)	Intermediate (I)	Resistant (R)	Susceptible (S)	Intermediate (I)	Resistant (R)
<i>Enterococci</i>	≤4	8 to 16 ^a	≥32	≥17 ^b	15 to 16 ^b	≤14 ^b
<i>Staphylococcus aureus</i> ^{c,d}	≤2	4 to 8	≥16	-	-	-
Coagulase-negative staphylococci ^{c,e}	≤4	8 to 16	≥32	-	-	-
<i>Streptococci</i> spp. other than <i>S. pneumoniae</i>	≤1 ^{f,g}	-	-	≥17 ^{f,h}	-	-

^a Isolates with vancomycin MICs of 8 to 16 mcg/mL should be further screened for vancomycin resistance using standardized procedures.^{1,2}

^b Plates should be held for a full 24 hours and examined using transmitted light. Measure the diameter of the zones of complete inhibition (as judged by the unaided eye), including the diameter of the disk. The zone margin should be considered the area showing no obvious, visible growth that can be detected with the unaided eye. Ignore faint growth of tiny colonies that can be detected only with a magnifying lens at the edge of the zone of inhibited growth. Any discernable growth within the zone of inhibition indicates vancomycin resistance. Organisms with intermediate zones should be tested by standardized dilution method.^{1,2}

^c Dilution testing should be performed to determine the susceptibility of all staphylococcal isolates. Disk diffusion testing is not reliable for testing vancomycin, as it does not differentiate vancomycin-susceptible isolates of *S. aureus* from vancomycin-intermediate isolates, nor does it differentiate among vancomycin-susceptible, intermediate, and resistant isolates of coagulase-negative staphylococci.²

^d Any *S. aureus* isolate for which the vancomycin MIC is ≥ 8 mcg/mL should be sent to a reference laboratory.²

^e Any coagulase-negative *Staphylococcus* isolate for which the vancomycin MIC is ≥ 32 mcg/mL, should be sent to a reference laboratory.²

^f The rare occurrence of resistant isolates precludes defining any results categories other than “Susceptible”. For isolates yielding results suggestive of a nonsusceptible category, organism identification and vancomycin susceptibility test results should be confirmed. If confirmed, isolates should be sent to a reference laboratory.²

^g Interpretative criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.^{1,2}

^h Interpretative criteria applicable only to tests performed by disk diffusion method using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO₂.³

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test. When tested against appropriate quality control strains, standard vancomycin powder should provide MIC values shown in Table 2. For the diffusion technique, the 30 mcg vancomycin disk should provide the zone diameters in Table 2 with the quality control strains:

Table 2. *In vitro* Susceptibility Test Quality Control Ranges for Vancomycin

Organism (ATCC#)	MIC range (mcg/mL)	Disk diffusion range (mm)
<i>Enterococcus faecalis</i> (29212)	1 to 4	Not applicable
<i>Staphylococcus aureus</i> (29213)	0.5 to 2	Not applicable
<i>Staphylococcus aureus</i> (25923) ^a	Not applicable	17 to 21
<i>Streptococcus pneumoniae</i> (49619) ^{b,c}	0.12 to 0.5	20 to 27

^a Quality control strain and interpretive criteria for testing vancomycin susceptibility of enterococci spp.

^b Interpretative criteria applicable only to test performed using cation-adjusted Mueller–Hinton broth with 2 to 5% lysed horse blood.¹ Disk diffusion interpretative criteria applicable only to tests performed using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO₂.²

^c Quality control strain and interpretive criteria for testing vancomycin susceptibility of *Streptococci* spp. other than *S. pneumoniae*.

INDICATIONS AND USAGE

Vancomycin hydrochloride for injection, USP is indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (β -lactam-resistant) staphylococci. It is indicated for penicillin-allergic patients, for patients who cannot receive or who have failed to respond to other drugs, including the penicillins or cephalosporins, and for infections caused by vancomycin-susceptible organisms that are resistant to other antimicrobial drugs. Vancomycin hydrochloride for injection, USP is indicated for initial therapy when methicillin-resistant staphylococci are suspected, but after susceptibility data are available, therapy should be adjusted accordingly.

Vancomycin hydrochloride for injection, USP is effective in the treatment of staphylococcal endocarditis. Its effectiveness has been documented in other infections due to staphylococci, including septicemia, bone infections, lower respiratory tract infections, skin and skin structure infections. When staphylococcal infections are localized and purulent, antibiotics are used as adjuncts to appropriate surgical measures.

Vancomycin hydrochloride for injection, USP has been reported to be effective alone or in combination with an aminoglycoside for endocarditis caused by *S. viridans* or *S. bovis*. For endocarditis caused by enterococci (e.g., *E. faecalis*), vancomycin has been reported to be effective only in combination with an aminoglycoside.

Vancomycin hydrochloride for injection, USP has been reported to be effective for the treatment of diphtheroid endocarditis. Vancomycin hydrochloride for injection, USP has been used successfully in combination with either rifampin, an aminoglycoside, or both in early-onset prosthetic valve endocarditis caused by *S. epidermidis* or diphtheroids.

Specimens for bacteriologic cultures should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to vancomycin.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of vancomycin hydrochloride for injection, USP and other antibacterial drugs, vancomycin hydrochloride for injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be

caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

The parenteral form of vancomycin hydrochloride may be administered orally for treatment of antibiotic-associated pseudomembranous colitis produced by *C. difficile* and for staphylococcal enterocolitis. Parenteral administration of vancomycin hydrochloride alone is of unproven benefit for these indications. Vancomycin is not effective by the oral route for other types of infection.

CONTRAINDICATIONS

Vancomycin hydrochloride for injection is contraindicated in patients with known hypersensitivity to this antibiotic

WARNINGS

Rapid bolus administration (e.g., over several minutes) may be associated with exaggerated hypotension, including shock and rarely cardiac arrest.

Vancomycin hydrochloride for injection should be administered in a diluted solution over a period of not less than 60 minutes to avoid rapid-infusion-related reactions. Stopping the infusion usually results in prompt cessation of these reactions.

Ototoxicity has occurred in patients receiving vancomycin hydrochloride for injection. It may be transient or permanent. It has been reported mostly in patients who have been given excessive doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Vancomycin should be used with caution in patients with renal insufficiency because the risk of toxicity is appreciably increased by high, prolonged blood concentrations.

Dosage of vancomycin hydrochloride for injection must be adjusted for patients with renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including vancomycin hydrochloride for injection, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General

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.

Prolonged use of vancomycin hydrochloride for injection may result in the overgrowth of nonsusceptible microorganisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken. In rare instances, there have been reports of pseudomembranous colitis due to *C. difficile* developing in patients who received intravenous vancomycin hydrochloride for injection.

In order to minimize the risk of nephrotoxicity when treating patients with underlying renal dysfunction or patients receiving concomitant therapy with an aminoglycoside, serial monitoring of renal function should be performed, and particular care should be taken in following appropriate dosing schedules (see DOSAGE AND ADMINISTRATION).

Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.

Reversible neutropenia has been reported in patients receiving vancomycin hydrochloride for injection (see ADVERSE REACTIONS). Patients who will undergo prolonged therapy with vancomycin hydrochloride for injection or those who are receiving concomitant drugs which may cause neutropenia should have periodic monitoring of the leukocyte count.

Vancomycin hydrochloride for injection is irritating to tissue and must be given by a secure IV route of administration. Pain, tenderness, and necrosis occur with intramuscular (IM) injection of vancomycin hydrochloride for injection or with inadvertent extravasation. Thrombophlebitis may occur, the frequency and severity of which can be minimized by administering the drug slowly as a dilute solution (2.5 to 5 g/L) and by rotation of venous access 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 agents. Infusion-related events may be minimized by the administration of vancomycin as a 60-minute infusion prior to anesthetic induction. The safety and efficacy of vancomycin administered by the intrathecal (intralumbar or intraventricular) route or by the intraperitoneal route have not been established by adequate and well controlled trials.

Although the safety and efficacy of vancomycin by the intraperitoneal route have not been established, reports have revealed that administration of sterile vancomycin by the intraperitoneal route during continuous ambulatory peritoneal dialysis (CAPD) has resulted in a syndrome of chemical peritonitis. To date, this syndrome has ranged from cloudy dialysate alone to a cloudy dialysate accompanied by variable degrees of abdominal pain and fever. This syndrome appears to be short-lived after discontinuation of intraperitoneal vancomycin.

Prescribing vancomycin hydrochloride for injection, USP in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

DRUG INTERACTIONS

Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing (see Pediatric Use under PRECAUTIONS) and anaphylactoid reactions (see ADVERSE REACTIONS).

Concurrent and/or sequential systemic or topical use of other potentially, neurotoxic and/or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymixin B, colistin, viomycin, or cisplatin, when indicated, requires careful monitoring.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of vancomycin hydrochloride for injection was found in standard laboratory tests. No definitive fertility studies have been performed.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Animal reproduction studies have not been conducted with vancomycin. It is not known whether vancomycin can affect reproduction capacity. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to vancomycin was noted. One infant whose mother received vancomycin in the third trimester experienced conductive hearing loss that was not attributed to the administration of vancomycin. Because the number of patients treated in this study was limited and vancomycin was administered only in the second and third trimesters, it is not known whether vancomycin causes fetal harm. Vancomycin should be given to a pregnant woman only if clearly needed.

Nursing Mothers

Vancomycin hydrochloride for injection is excreted in human milk. Caution should be exercised when vancomycin hydrochloride for injection is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

In pediatric patients, it may be appropriate to confirm desired vancomycin serum concentrations. Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing in pediatric patients (see PRECAUTIONS).

Geriatric Use

The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted. Vancomycin dosage schedules should be adjusted in elderly patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Patients should be counseled that antibacterial drugs including vancomycin hydrochloride for injection, USP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When vancomycin hydrochloride for injection, USP is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by vancomycin hydrochloride for injection, USP or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

ADVERSE REACTIONS

Infusion-Related Events

During or soon after rapid infusion of vancomycin hydrochloride for injection, patients may develop anaphylactoid reactions, including hypotension (see ANIMAL PHARMACOLOGY), wheezing, dyspnea, urticaria, or pruritus. Rapid infusion may also cause flushing of the upper body (“red neck”) or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may

persist for several hours. Such events are infrequent if vancomycin hydrochloride for injection is given by a slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when vancomycin hydrochloride for injection was administered at a rate of 10 mg/min or less.

Nephrotoxicity

Renal failure, principally manifested by increased serum creatinine or BUN concentrations, especially in patients administered large doses of vancomycin, has been reported rarely. Cases of interstitial nephritis have also been reported rarely. Most of these have occurred in patients who were given aminoglycosides concomitantly or who had preexisting kidney dysfunction. When vancomycin was discontinued, azotemia resolved in most patients.

Gastrointestinal

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS) (Appears prior to Ototoxicity in the NDA).

Ototoxicity

A few dozen cases of hearing loss associated with vancomycin have been reported. Most of these patients had kidney dysfunction or a preexisting hearing loss or were receiving concomitant treatment with an ototoxic drug. Vertigo, dizziness, and tinnitus have been reported rarely.

Hematopoietic

Reversible neutropenia, usually starting 1 week or more after onset of therapy with vancomycin or after a total dosage of more than 25 g, has been reported for several dozen patients. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been reported. Although a causal relationship has not been established, reversible agranulocytosis (granulocytes $<500/\text{mm}^3$) has been reported rarely.

Phlebitis

Inflammation at the injection site has been reported.

Miscellaneous

Infrequently, patients have been reported to have had anaphylaxis, drug fever, nausea, chills, eosinophilia, rashes including exfoliative dermatitis, linear IgA bullous dermatosis, Stevens-Johnson syndrome, toxic epidermal necrolysis and vasculitis in association with the administration of vancomycin.

Chemical peritonitis has been reported following intraperitoneal administration (see PRECAUTIONS)

POST MARKETING REPORTS

The following adverse reactions have been identified during post-approval use of vancomycin. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

To report SUSPECTED ADVERSE EVENTS, contact Xellia Pharmaceuticals at safety@xellia.com or 1-855-642-2594, or FDA at 1-800-FDA-1088 or www.fda.gov.

OVERDOSAGE

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Hemofiltration and hemoperfusion with polysulfone resin have been reported to result in

increased vancomycin clearance. The median lethal intravenous dose is 319 mg/kg in rats and 400 mg/kg in mice.

To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR). In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

DOSAGE & ADMINISTRATION

Infusion-related events are related to both the concentration and the rate of administration of vancomycin. Concentrations of no more than 5 mg/mL and rates of no more than 10 mg/min, are recommended in adults (see also age-specific recommendations). In selected patients in need of fluid restriction, a concentration up to 10 mg/mL may be used; use of such higher concentrations may increase the risk of infusion-related events. An infusion rate of 10 mg/min or less is associated with fewer infusion-related events (see ADVERSE REACTIONS). Infusion-related events may occur, however, at any rate or concentration.

Patients With Normal Renal Function

Adults

The usual daily intravenous dose is 2 g divided either as 500 mg every 6 hours or 1 g 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. Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose.

Pediatric patients

The usual intravenous dosage of vancomycin is 10 mg/kg per dose given every 6 hours. Each dose should be administered over a period of at least 60 minutes. Close monitoring of serum concentrations of vancomycin may be warranted in these patients.

Neonates

In pediatric patients up to the age of 1 month, the total daily intravenous dosage may be lower. In neonates, an initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the 1st week of life and every 8 hours thereafter up to the age of 1 month. Each dose should be administered over 60 minutes. In premature infants, vancomycin clearance decreases as postconceptional age decreases. Therefore, longer dosing intervals may be necessary in premature infants. Close monitoring of serum concentrations of vancomycin is recommended in these patients.

Patients With Impaired Renal Function and Elderly Patients

Dosage adjustment must be made in patients with impaired renal function. In premature infants and the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Measurement of vancomycin serum concentrations can be helpful in optimizing therapy, especially in seriously ill patients with changing renal function. Vancomycin serum concentrations can be determined by use of microbiologic assay, radioimmunoassay, fluorescence polarization immunoassay, fluorescence immunoassay, or high-pressure liquid chromatography. If creatinine clearance can be measured or estimated accurately, the dosage for most patients with renal impairment can be calculated using the following table. The dosage of vancomycin hydrochloride for injection per day in mg is about 15 times the glomerular filtration rate in mL/min (see following table).

DOSAGE TABLE FOR VANCOMYCIN IN PATIENTS WITH IMPAIRED RENAL FUNCTION

(As adapted from Moellering et al.⁴)

Creatinine Clearance mL/min	Vancomycin Dose mg/24 h
100	1,545
90	1,390
80	1,235
70	1,080
60	925
50	770
40	620
30	465
20	310
10	155

The initial dose should be no less than 15 mg/kg, even in patients with mild to moderate renal insufficiency. The table is not valid for functionally anephric patients. For such patients, an initial dose of 15 mg/kg of body weight should be given to achieve prompt therapeutic serum concentrations. The dose required to maintain stable concentrations is 1.9 mg/kg/24 hr. In patients with marked renal impairment, it may be more convenient to give maintenance doses of 250 to 1,000 mg once every several days rather than administering the drug on a daily basis. In anuria, a dose of 1,000 mg every 7 to 10 days has been recommended. When only serum creatinine is known, the following formula (based on sex, weight and age of the patient) may be used to calculate creatinine clearance. Calculated creatinine clearances (mL/min) are only estimates. The creatinine clearance should be measured promptly.

Men:
$$\frac{[\text{Weight (kg)} \times (140 - \text{age in years})]}{72 \times \text{serum creatinine concentration (mg/dL)}}$$

Women: 0.85 x above value

The serum creatinine must represent a steady state of renal function. Otherwise, the estimated value for creatinine clearance is not valid. Such a calculated clearance is an overestimate of actual clearance in patients with conditions: (1) characterized by decreasing renal function, such as shock, severe heart failure, or oliguria; (2) in which a normal relationship between muscle mass and total body weight is not present, such as in obese patients or those with liver disease, edema, or ascites; and (3) accompanied by debilitation, malnutrition, or inactivity. The safety and efficacy of vancomycin administration by the intrathecal (intralumbar or intraventricular) routes have not been established. Intermittent infusion is the recommended method of administration.

Compatibility with Other Drugs and IV Fluids

The following diluents are physically and chemically compatible (with 4 g/L vancomycin hydrochloride):

5% Dextrose Injection, USP

5% Dextrose Injection and 0.9% Sodium Chloride Injection, USP

Lactated Ringer's Injection, USP

5% Dextrose and Lactated Ringer's Injection

Normosol®-M and 5% Dextrose

0.9% Sodium Chloride Injection, USP

Isolyte® E

Good professional practice suggests that compounded admixtures should be administered as soon after preparation as is feasible.

Vancomycin solution has a low pH and may cause physical instability of other compounds.

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 the administration of these antibiotics. It is also recommended to dilute solutions of vancomycin to 5 mg/mL or less.

Although intravitreal injection is not an approved route of administration for vancomycin, precipitation has been reported after intravitreal injection of vancomycin and ceftazidime for endophthalmitis using different syringes and needles. The precipitates dissolved gradually, with complete clearing of the vitreous cavity over two months and with improvement of visual acuity.

PREPARATION AND STABILITY

Directions for Proper Use of a Pharmacy Bulk Package

Not for direct infusion. The pharmacy bulk package is for use in the Pharmacy Admixture Service only in a suitable work area such as a laminar flow hood. Using aseptic technique, the closure may be penetrated only one time after reconstitution using a suitable sterile transfer device or dispensing set, which allows measured dispensing of the contents. Use of a syringe and needle is not recommended as it may cause leakage. After entry, use entire contents of the Pharmacy Bulk Package bottle promptly. The entire contents of the Pharmacy Bulk Package bottle should be dispensed within 4 hours after initial entry. A maximum time of 4 hours from the initial entry may be allowed to complete fluid aliquoting/transferring operations. Discard the container no later than 4 hours after initial closure puncture. This time limit should begin with the introduction of solvent or diluent into the Pharmacy Bulk Package bottle.

Preparation and Stability

5 g Pharmacy Bulk Package bottle

At the time of use, reconstitute by adding 100 mL of Sterile Water for Injection to the 5 g Pharmacy Bulk Package bottle of dry, sterile vancomycin powder. The resultant solution will contain vancomycin equivalent to 500 mg/10 mL. FURTHER DILUTION IS REQUIRED. Reconstituted solutions of vancomycin (500 mg/10 mL) must be further diluted in at least 100 mL of a suitable infusion solution. Doses of 1 gram/20 mL must be further diluted in at least 200 mL of a suitable infusion solution. The desired dose diluted in this manner should be administered by intermittent intravenous infusion over a period of at least 60 minutes.

10 g Pharmacy Bulk Package bottle

At the time of use, reconstitute by adding 95 mL of Sterile Water for Injection, USP to the 10 g bottle of dry, sterile vancomycin powder. The resultant solution will contain vancomycin equivalent to 500 mg/5 mL (1 g/10 mL). AFTER RECONSTITUTION, FURTHER DILUTION IS REQUIRED.

Reconstituted solutions of vancomycin (500 mg/5 mL) must be further diluted in at least 100 mL of a suitable infusion solution. For doses of 1 gram (10 mL), at least 200 mL of solution must be used. The desired dose diluted in this manner should be administered by intermittent IV infusion over a period of at least 60 minutes.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.

For Oral Administration

Oral vancomycin is used in treating antibiotic-associated pseudomembranous colitis caused by *C. difficile* and for staphylococcal enterocolitis. Vancomycin is not effective by the oral route for other types of infections. The usual adult total daily dosage is 500 mg to 2 g given in 3 or 4 divided doses for 7 to 10 days. The total daily dose in children is 40 mg/kg of body weight in 3 or 4 divided doses for 7 to 10 days. The total daily dosage should not exceed 2 g. The appropriate dose may be diluted in 1 oz of water and given to the patients to drink. Common flavoring syrups may be added to the solution to

improve the taste for oral administration. The diluted solution may be administered via a nasogastric tube.

HOW SUPPLIED

NDC No.

45932-0031-1 Vancomycin Hydrochloride for Injection, USP 5 g vancomycin in a Pharmacy Bulk Package Bottle 100mL, packaged individually

45932-0032-1 Vancomycin Hydrochloride for Injection, USP 10 g vancomycin in a Pharmacy Bulk Package Bottle 100mL, packaged individually

Store dry powder at 20° to 25°C (68° to 77°F) [see USP Controlled Room temperature] in original container.

Bottle stopper is not made with natural rubber latex.

ANIMAL PHARMACOLOGY

In animal studies, hypotension and bradycardia occurred in dogs receiving an intravenous infusion of vancomycin hydrochloride 25 mg/kg, at a concentration of 25 mg/mL and an infusion rate of 13.3 mL/min.

REFERENCES

1. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Eighth ed., CLSI document M07-A8. Clinical and Laboratory Standards Institute. Wayne, PA. January, 2009.
2. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement, CLSI document M100-S21. Clinical and Laboratory Standards Institute. Wayne, PA. January, 2011.
3. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard – Tenth ed., CLSI document M02-A10. Clinical and Laboratory Standards Institute. Wayne, PA. January, 2009.
4. Moellering RC, Krogstad DJ, Greenblatt DJ: Vancomycin therapy in patients with impaired renal function: A nomogram for dosage. *Ann Intern Med* 1981;94:343.

Manufactured by

Xellia Pharmaceuticals ApS

Dalslandsgade 11

2300 Copenhagen S

Denmark

Revised: September 2015

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 45932-0031-1

Vancomycin Hydrochloride
for injection, USP
**5 grams* per Pharmacy
Bulk Package**
PHARMACY BULK PACKAGE
- NOT FOR DIRECT INFUSION
For Intravenous Infusion After Dilution
AFTER RECONSTITUTION
MUST BE FURTHER DILUTED.
NOT TO BE DISPENSED AS A UNIT.
Lyophilized Rx only

NDC 45932-0031-1

**Vancomycin Hydrochloride
for Injection, USP**

**5 grams* per Pharmacy
Bulk Package**

**PHARMACY BULK PACKAGE
- NOT FOR DIRECT INFUSION**

For Intravenous Infusion After Dilution

**AFTER RECONSTITUTION
MUST BE FURTHER DILUTED.
NOT TO BE DISPENSED AS A UNIT.**

Lyophilized

Rx only

Sterile, Nonpyrogenic. Preservative Free.
**READ INSERT FOR PRECAUTIONS AND
DIRECTIONS BEFORE USE. *Each
pharmacy bulk package bottle contains:**
Vancomycin hydrochloride equivalent to 5 g
vancomycin. **Usual Adult Dosage:** 2 g daily,
in divided doses. **Important:** Read package
insert for **PRECAUTIONS** and **DIRECTIONS
FOR USE. Prior to reconstitution, store at
20° to 25°C (68° to 77°F)** [See USP Controlled
Room Temperature]. **After reconstitution,**
use promptly. (Discard container within **4 hours**
after entry). See package insert for full informa-
tion. **DIRECTIONS FOR USE:** This pharmacy
bulk package is for use in a Pharmacy
Admixture Service. Penetrate one time after
reconstitution using a sterile dispensing set.
Reconstitute with 100 mL of Sterile Water for
Injection using aseptic technique. The resulting
solution will contain vancomycin equivalent to
500 mg/10 mL. **MUST BE FURTHER DILUTED
BEFORE USE.** Dispense aliquots from the
bottle using a suitable sterile dispensing set
into infusion fluids under a laminar flow hood
using aseptic technique. **DISCARD BOTTLE
NO LATER THAN 4 HOURS AFTER INITIAL
ENTRY** (see package insert).

VANCOMYCIN HYDROCHLORIDE FOR INJECTION, USP

Discard after Date _____ and Time _____

Xellia Pharmaceuticals ApS, Made in Denmark.

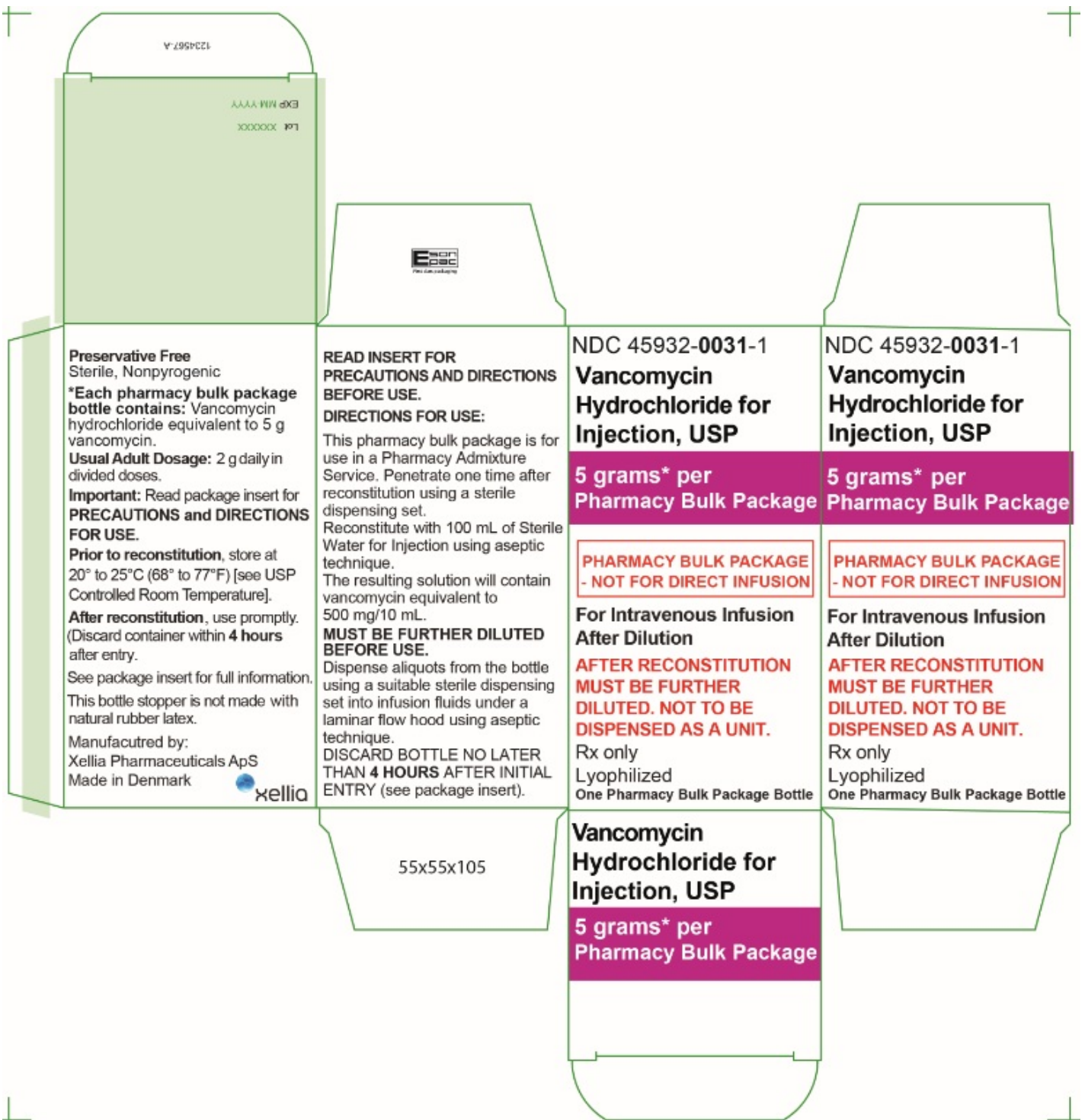
6 7 0 0 0 4 0 8 8 2 9 0 1 (T O)



K123456-A

Lot:

Exp:



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 45932-0032-1

Vancomycin Hydrochloride
for injection, USP

**10 grams* per Pharmacy
Bulk Package**

PHARMACY BULK PACKAGE
- NOT FOR DIRECT INFUSION

For Intravenous Infusion After Dilution
AFTER RECONSTITUTION
MUST BE FURTHER DILUTED.
NOT TO BE DISPENSED AS A UNIT.
Lyophilized Rx only

NDC 45932-0032-1

**Vancomycin Hydrochloride
for Injection, USP**

**10 grams* per
Pharmacy Bulk Package**

**PHARMACY BULK PACKAGE
- NOT FOR DIRECT INFUSION**

For Intravenous Infusion After Dilution

**AFTER RECONSTITUTION
MUST BE FURTHER DILUTED.
NOT TO BE DISPENSED AS A UNIT.**

Lyophilized

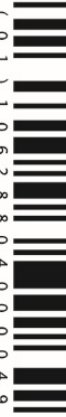
Rx only

Sterile. Nonpyrogenic. Preservative Free.
READ INSERT FOR PRECAUTIONS AND DIRECTIONS BEFORE USE. *Each pharmacy bulk package bottle contains: Vancomycin hydrochloride equivalent to 10 g in divided doses. **Usual Adult Dosage:** 2 g daily, insert for **PRECAUTIONS** and **DIRECTIONS FOR USE.** **Prior to reconstitution,** store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. **After reconstitution,** use promptly. (Discard container within **4 hours** after entry). See package insert for full information. **DIRECTIONS FOR USE:** This pharmacy bulk package is for use in a Pharmacy Admixture Service. Penetrate one time after reconstitution using a sterile dispensing set. Reconstitute with 95 mL of Sterile Water for Injection using aseptic technique. Each 5 mL of the resulting solution contains 500 mg of Vancomycin, and each 10 mL of the resulting solution contains 1 g of Vancomycin. **MUST BE FURTHER DILUTED BEFORE USE.** Dispense aliquots from the bottle using a suitable sterile dispensing set into infusion fluids under a laminar flow hood using aseptic technique. **DISCARD BOTTLE NO LATER THAN 4 HOURS AFTER INITIAL ENTRY** (see package insert).

VANCOMYCIN HYDROCHLORIDE FOR INJECTION, USP

Discard after Date _____ and Time _____

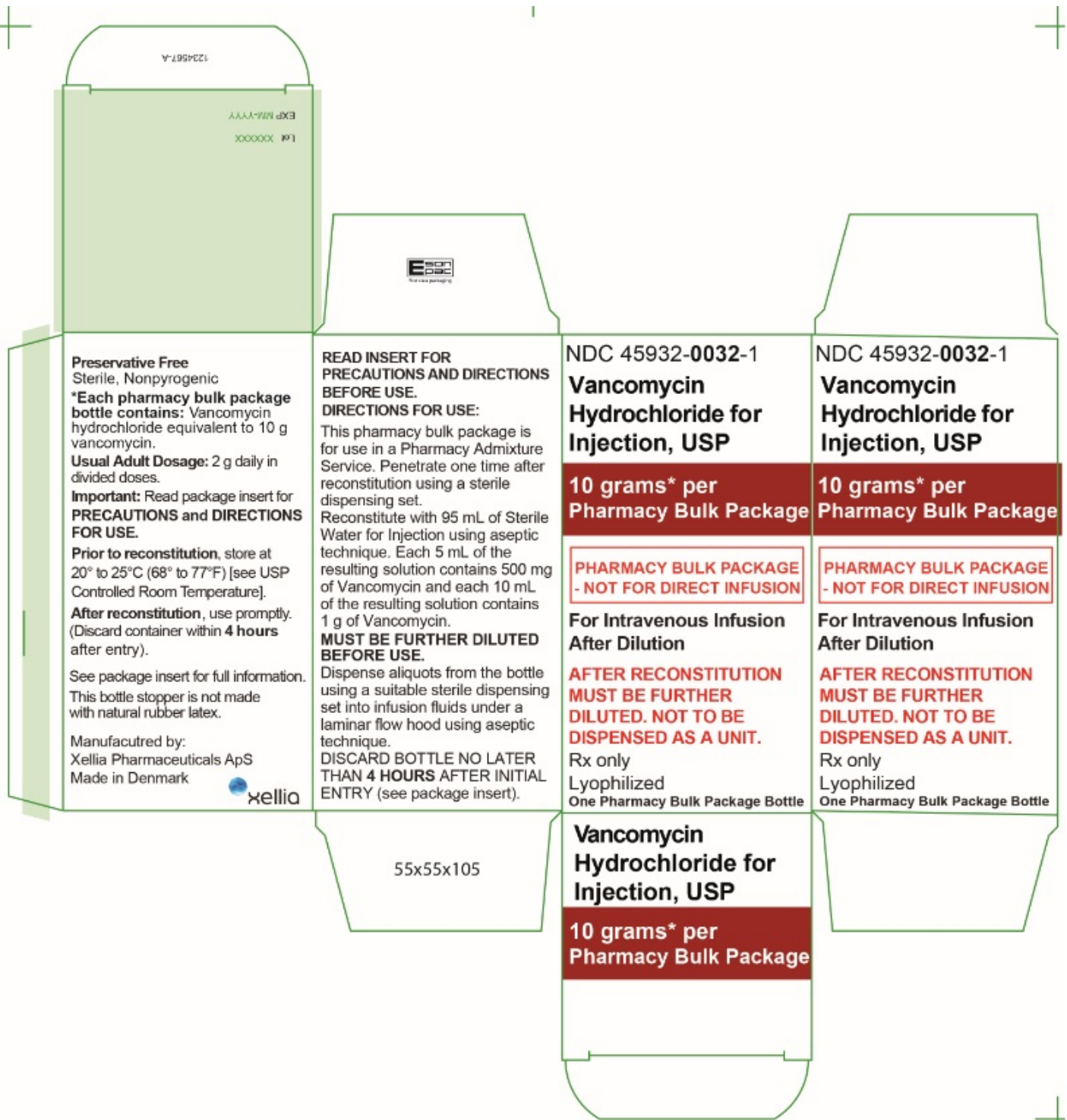
Xellia Pharmaceuticals ApS, Made in Denmark
6 4 0 0 0 4 0 8 2 9 0 1 (1 0)



K123456-A

Lot:

Exp:



VANCOMYCIN HYDROCHLORIDE

vancomycin hydrochloride injection

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:45932-0031
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name		Basis of Strength	Strength
VANCOMYCIN HYDROCHLORIDE (UNII: 71WO621TJD) (VANCOMYCIN - UNII:6Q205EH1VU)		VANCOMYCIN	5 g in 100 mL

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:45932-0031-1	1 in 1 CARTON		
1		100 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA206243	02/10/2015	

VANCOMYCIN HYDROCHLORIDE			
vancomycin hydrochloride injection			

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:45932-0032
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
VANCOMYCIN HYDROCHLORIDE (UNII: 71WO621TJD) (VANCOMYCIN - UNII:6Q205EH1VU)	VANCOMYCIN	10 g in 100 mL

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:45932-0032-1	1 in 1 CARTON		
1		100 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA206243	02/10/2015	

Labeler - Xellia Pharmaceuticals ApS (305814345)

Establishment			
Name	Address	ID/FEI	Business Operations

Revised: 12/2015

Xellia Pharmaceuticals ApS