

VANCOMYCIN HYDROCHLORIDE - vancomycin hydrochloride injection, powder, lyophilized, for solution
Xellia Pharmaceuticals, ApS

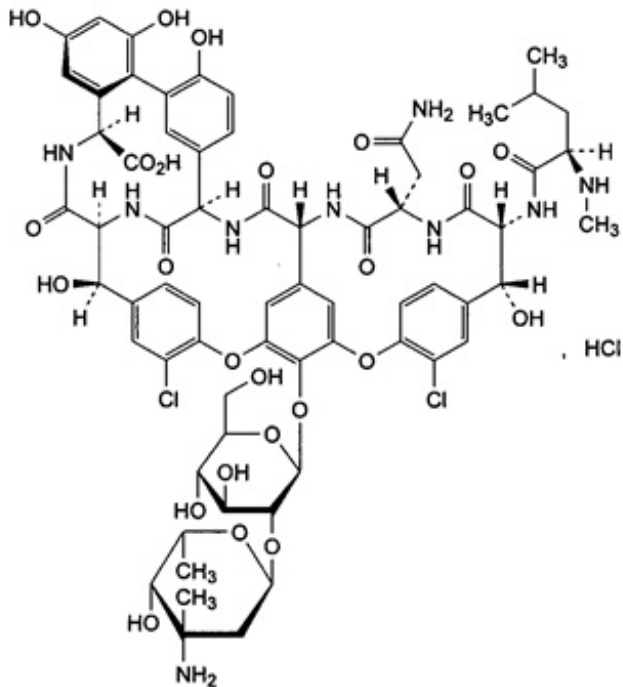
VANCOMYCIN HYDROCHLORIDE FOR INJECTION, USP
Rx only

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 vials each containing the equivalent of 500 mg or 1 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, 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**). **AFTER RECONSTITUTION FURTHER DILUTION IS REQUIRED BEFORE USE.**

Vancomycin Hydrochloride for Injection, USP is a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*). The chemical name for vancomycin hydrochloride is (S_a)-(3S,6R,7R,22R,23S,26S,36R,38aR)-44-[[2-O-(3-Amino-2,3,6-trideoxy-3-C-methyl- α -L-lyxo-hexopyranosyl)- β -D-glucopyranosyl]oxy]-3-(carbamoylmethyl)-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-[(2R)-4-methyl-2-(methylamino)]valeramido]-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. Vancomycin hydrochloride has the following structural formula:



$C_{66}H_{75}Cl_2N_9O_{24} \cdot HCl$

1485.73

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 two 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 two hours after infusion, and mean plasma concentrations of about 10 mcg/mL six 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 four to six 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 six 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 intravenous 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 susceptibility of organisms to vancomycin. Interpretation involves the 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

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

^a Isolates with vancomycin MIC's 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 test 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 test 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 the 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 strain.

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)	1-4	Not applicable
<i>Staphylococcus aureus</i> (29213)	0.5-2	Not applicable
<i>Staphylococcus aureus</i> (25923) ^a	Not applicable	17-21
<i>Streptococcus pneumoniae</i> (49619) ^{b,c}	0.12-0.5	20-27

^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 & USAGE

Vancomycin is indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (beta-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 is indicated for initial therapy when methicillin-resistant staphylococci are suspected, but after susceptibility data are available, therapy should be adjusted accordingly.

Vancomycin 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 has been reported to be effective alone or in combination with an aminoglycoside for endocarditis caused by *Streptococcus 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 has been reported to be effective for the treatment of diphtheroid endocarditis. Vancomycin 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 and other antibacterial drugs, vancomycin 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 for Injection, USP 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, USP 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 should be administered 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.

Ototoxicity has occurred in patients receiving Vancomycin Hydrochloride for Injection USP. 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, USP 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, USP 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 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 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.

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 (see ADVERSE REACTIONS). Patients who will undergo prolonged therapy with vancomycin or those who are receiving concomitant drugs which may cause neutropenia should have periodic monitoring of the leukocyte count. Vancomycin is irritating to tissue and must be given by a secure intravenous route of administration. Pain, tenderness and necrosis occur with intramuscular (IM) injection of Vancomycin Hydrochloride for Injection, USP 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 rotating 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 administration by the intrathecal (intralumbar or intraventricular) route or by the intraperitoneal route have not been established by adequate and well-controlled trials.

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 a 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 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.

Information for Patients

Patients should be counseled that antibacterial drugs including vancomycin, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When vancomycin is prescribed to treat 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 or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotics 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.

Drug Interactions

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

Concurrent and/or sequential systematic 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, USP 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 is excreted in human milk. Caution should be exercised when vancomycin is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or 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**).

Geriatrics

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**).

ADVERSE REACTIONS

Infusion-Related Events

During or soon after rapid infusion of vancomycin, 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 is given by slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when vancomycin 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.

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.

Gastrointestinal

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

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 of vancomycin (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 ApS - Toll free number: 1-855-642-2594/Email: safety@xellia.com or FDA at 1-800-FDA-1088 or <http://www.fda.gov> / for voluntary reporting of adverse reactions.

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 patients.

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 per day in mg is about 15 times the glomerular filtration rate in mL/min (see table below).

**Dosage table for
vancomycin in patients with
impaired renal function**
(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 h. 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 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.

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 × 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 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.

Preparation and Stability

At the time of use, reconstitute the vials of Vancomycin Hydrochloride for Injection, USP with Sterile Water for Injection, USP to a concentration of 50 mg of vancomycin/mL (see following table for

volume of diluent.)

Concentration/Vial	Volume of Diluent
500 mg	10 mL
1 g	20 mL

After reconstitution, the vials may be stored in a refrigerator for 96 hours without significant loss of potency.

Reconstituted solutions of vancomycin (500mg/10mL) must be further diluted in at least 100 mL of a suitable infusion solution. For doses of 1 gram (20 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.

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.

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 patient 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

Vancomycin Hydrochloride for Injection, USP equivalent to 500 mg vancomycin in a 10 mL flip-top vial, in packages of 1.

NDC 45932-0028-1

Vancomycin Hydrochloride for Injection, USP equivalent to 500 mg vancomycin in a 10 mL flip-top vial, in packages of 10.

NDC 45932-0028-2

Vancomycin Hydrochloride for Injection, USP equivalent to 1 g vancomycin in a 20 mL flip-top vial, in packages of 1.

NDC 45932-0029-1

Vancomycin Hydrochloride for Injection, USP equivalent to 1 g vancomycin in a 20 mL flip-top vial, in packages of 10.

NDC 45932-0029-2

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Vial stoppers do not contain 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 Test 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 Inter Med* 1981;94:343.

Xellia Pharmaceuticals ApS

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Denmark

xellia

Revised April 2014

PACKAGE LABEL PRINCIPAL DISPLAY PANEL - VANCOMYCIN HYDROCHLORIDE FOR INJECTION, USP - 500mg

NDC 45932-0028-1

**Vancomycin
Hydrochloride
for Injection, USP**

500 mg*/vial

For Intravenous Use

**MUST BE FURTHER
DILUTED BEFORE
USE. SEE INSERT.**

Rx only

IMPORTANT: READ INSERT FOR PRECAUTIONS AND DIRECTIONS BEFORE USE.

Sterile, Lyophilized. **Preservative Free.**

*Each vial contains: Vancomycin hydrochloride equivalent to 500 mg vancomycin.

Usual Adult Dosage: 2 g daily in divided doses.

Dilute contents of the vial with 10 mL Sterile

Water for Injection. **Prior to reconstitution,**

store at 20° to 25°C (68° to 77°F) [see USP

Controlled Room Temperature].

After reconstitution, this vial may be stored in a refrigerator for 96 hours without significant

loss of potency. Made in Denmark.

Manufactured by: Xellia Pharmaceuticals ApS



XXXXXX-A

Lot XXXXXX

EXP MM-YYYY

Varnish Free Area

6040009

EXP MM-YY

Lot XXXXX

NDC 45932-0028-1

Vancomycin Hydrochloride for Injection, USP

500 mg*/vial

For Intravenous Use

MUST BE FURTHER DILUTED BEFORE USE. SEE INSERT.

Rx only

IMPORTANT: READ INSERT FOR PRECAUTIONS AND DIRECTIONS BEFORE USE

One 500 mg vial

IMPORTANT: READ INSERT FOR PRECAUTIONS AND DIRECTIONS BEFORE USE.

Sterile, Lyophilized.

Preservative Free.

*Each vial contains: Vancomycin hydrochloride equivalent to 500 mg vancomycin.

Manufactured by: Xellia Pharmaceuticals ApS. Made in Denmark.



XXXX-XXXX-XX X

NDC 45932-0028-1

Vancomycin Hydrochloride for Injection, USP

500 mg*/vial

For Intravenous Use

MUST BE FURTHER DILUTED BEFORE USE. SEE INSERT.

Rx only

IMPORTANT: READ INSERT FOR PRECAUTIONS AND DIRECTIONS BEFORE USE

One 500 mg vial

Usual Adult Dosage: 2 g daily in divided doses.

Dilute contents of the vial with 10 mL Sterile Water for Injection.

Prior to reconstitution, store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

After reconstitution, this vial may be stored in a refrigerator for 96 hours without significant loss of potency.

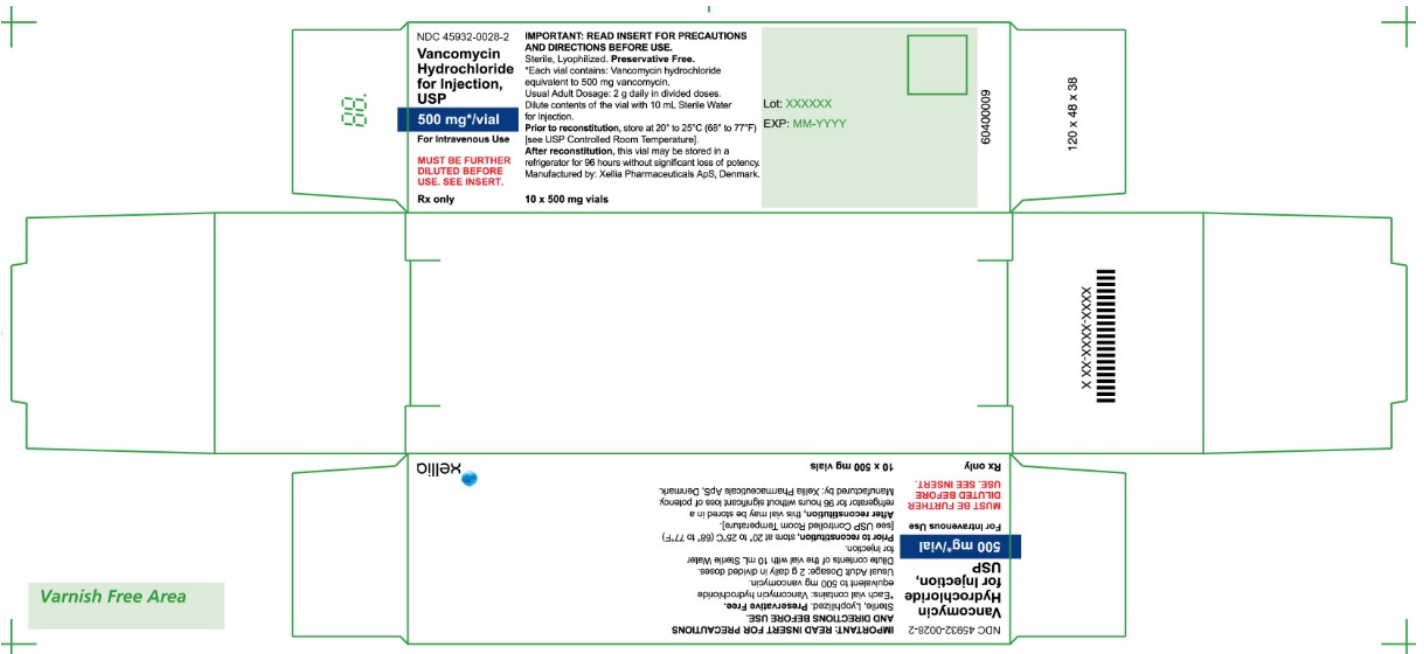


37x37x72


Vancomycin Hydrochloride for Injection, USP

500 mg*/vial

88.



PACKAGE LABEL PRINCIPAL DISPLAY PANEL - VANCOMYCIN HYDROCHLORIDE FOR INJECTION, USP - 1g

<p>NDC 45932-0029-1</p> <p>Vancomycin Hydrochloride for Injection, USP</p> <p>1 g*/vial</p> <p>For Intravenous Use</p> <p>MUST BE FURTHER DILUTED BEFORE USE. SEE INSERT.</p> <p>Rx only</p>	<p>IMPORTANT: READ INSERT FOR PRECAUTIONS AND DIRECTIONS BEFORE USE.</p> <p>Sterile, Lyophilized. Preservative Free.</p> <p>*Each vial contains: Vancomycin hydrochloride equivalent to 1 g vancomycin.</p> <p>Usual Adult Dosage: 2 g daily in divided doses. Dilute contents of the vial with 20 mL Sterile Water for Injection. Prior to reconstitution, store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. After reconstitution, this vial may be stored in a refrigerator for 96 hours without significant loss of potency. Made in Denmark.</p> <p>Manufactured by: Xellia Pharmaceuticals ApS</p>	 <p>0 12345-679-12 0</p> <p>XXXXXX-A</p> <p>Lot XXXXXX</p> <p>EXP MM-YYYY</p>
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Varnish Free Area

6040007

EXP MM-YY
Lot XXXXX

NDC 45932-0029-1
Vancomycin Hydrochloride for Injection, USP

1 g*/vial

For Intravenous Use
MUST BE FURTHER DILUTED BEFORE USE. SEE INSERT.

Rx only
IMPORTANT: READ INSERT FOR PRECAUTIONS AND DIRECTIONS BEFORE USE

One 1 g vial

IMPORTANT: READ INSERT FOR PRECAUTIONS AND DIRECTIONS BEFORE USE.

Sterile, Lyophilized.

Preservative Free.

*Each vial contains: Vancomycin hydrochloride equivalent to 1 g vancomycin.

Manufactured by: Xellia Pharmaceuticals ApS. Made in Denmark.



NDC 45932-0029-1
Vancomycin Hydrochloride for Injection, USP

1 g*/vial

For Intravenous Use
MUST BE FURTHER DILUTED BEFORE USE. SEE INSERT.

Rx only
IMPORTANT: READ INSERT FOR PRECAUTIONS AND DIRECTIONS BEFORE USE

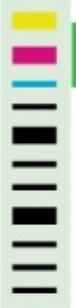
One 1 g vial

Usual Adult Dosage: 2 g daily in divided doses.

Dilute contents of the vial with 20 mL Sterile Water for Injection.

Prior to reconstitution, store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

After reconstitution, this vial may be stored in a refrigerator for 96 hours without significant loss of potency.

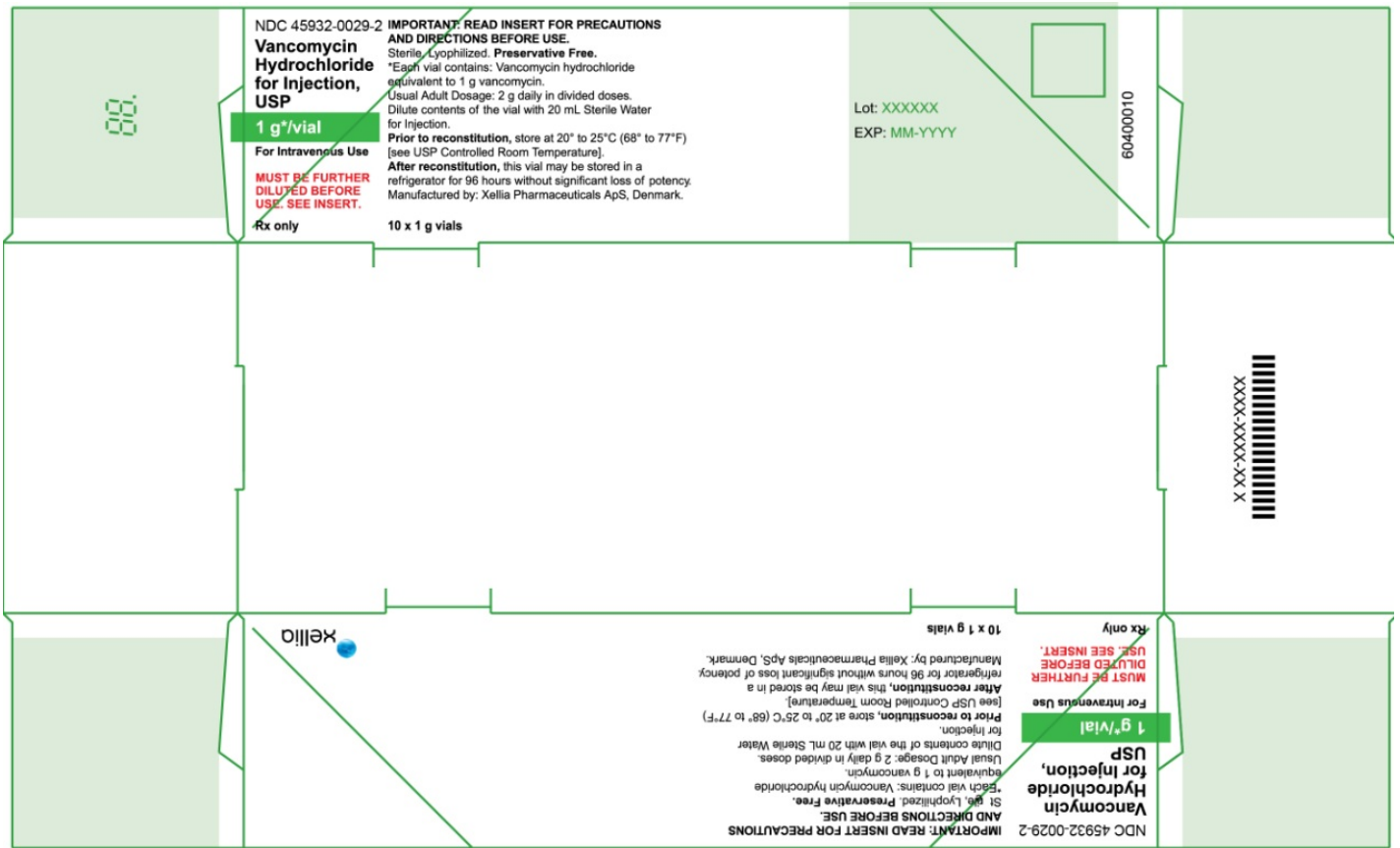


37x37x72

Vancomycin Hydrochloride for Injection, USP

1 g*/vial

88.



VANCOMYCIN HYDROCHLORIDE

vancomycin hydrochloride injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:45932-0028
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety			
Ingredient Name	Basis of Strength	Strength	
VANCOMYCIN HYDROCHLORIDE (UNII: 71WO621TJD) (VANCOMYCIN - UNII:6Q205EH1VU)	VANCOMYCIN	500 mg	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:45932-0028-1	1 in 1 CARTON; Type 0: Not a Combination Product		
2	NDC:45932-0028-2	10 in 1 CARTON; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091377	04/10/2014	

VANCOMYCIN HYDROCHLORIDE

vancomycin hydrochloride injection, powder, lyophilized, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:45932-0029
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VANCOMYCIN HYDROCHLORIDE (UNII: 71WO621TJD) (VANCOMYCIN - UNII:6Q205EH1VU)	VANCOMYCIN	1 g

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:45932-0029-1	1 in 1 CARTON; Type 0: Not a Combination Product		
2	NDC:45932-0029-2	10 in 1 CARTON; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091377	04/10/2014	

Labeler - Xellia Pharmaceuticals, ApS (305814345)

Establishment

Name	Address	ID/FEI	Business Operations
Xellia Pharmaceuticals, ApS		305814345	MANUFACTURE(45932-0028, 45932-0029)

Revised: 12/2015

Xellia Pharmaceuticals, ApS