Executive Summary: VANCO READY™ Premix Vancomycin Injection, USP Product Profiler

About VANCO READY™

VANCO READY is the first and only room temperature premix intravenous (IV) vancomycin agent currently available in the United States. VANCO READY is a novel premix ready to use (RTU) IV formulation of vancomycin that received FDA approval for use in adults and children (1 month and older) on February 19, 2019.[1,2] This profiler also examines various considerations related to the optimal management of gram-positive infections and the implementation of VANCO READY, in relation to the Boxed Warning.

WARNING: RISK OF EMBRYO-FETAL TOXICITY DUE TO EXCIPIENTS

This formulation of Vancomycin Injection, USP is not recommended for use during pregnancy because it contains the excipients polyethylene glycol (PEG) 400 and N-acetyl-D-alanine (NADA), which caused fetal malformations in animal reproduction studies. If use of vancomycin is needed during pregnancy, use other available formulations of vancomycin.

A Focus on Septicemia

Gram-positive bacterial infections represent a significant proportion (47%) of septicemia-related infections as well as other types of infections at high risk for triggering septicemia.[3]

Septicemia is among one of the infection categories currently indicated for use of vancomycin. Other infection categories include: infective endocarditis, skin and skin structure infections, bone infections, and lower respiratory tract infections.[1]

Key Sepsis Facts

Sepsis is among the most expensive conditions treated and **a leading cause of death** in US hospitals[4-6]

1.7 million Americans develop sepsis each year[6]

The risk of death from sepsis increases by **as much as 7.6% for every hour** that treatment is delayed[7]

Importance of Time to Treat

According to Centers for Medicare & Medicaid Services (CMS) data, only 57% of Medicare patients receive appropriate sepsis care.[8]

Delays in treatment may be a result of procedural, operational, and/or compounding-related barriers.

These barriers can include:

- Poor adherence to current sepsis diagnostic and treatment protocols[9]
- Drug shortages and quality control problems[10,11]
- Hospital supply-chain disruptions, including[12-14]
  - Lack of sepsis protocol in electronic medical record (EMR) systems
  - Wait time for drug delivery from the central pharmacy due to the lack of RTU formulation available at the patient care area
  - Wait time for compounding of the medication
  - Delays related to nursing medication preparation skills/training
- Lack of RTU antibiotics in the emergency department (ED)[15]
  - Results have been shown when RTU antibiotics are not optimized in the ED, treatment delays of up to 154 minutes have been documented (from the time of the patient arrival to the patient receiving the medication)

Delays in treatment have also led to an increased risk of mortality among patients with sepsis. Multiple studies have found that suboptimal management of sepsis can lead to increased mortality, especially when treatment with effective antibiotics is delayed in patients already demonstrating one or more sepsis-related symptoms. These studies determined that every 1-hour delay past a patient's arrival in the ED with sepsis increases the patient's odds of death.[7,16]

Research supports that removing these barriers, changing protocols, improving drug-stocking practices, and re-educating relevant clinical staff can help reduce delays in patients receiving effective treatments in a timely manner.[15] All of these barriers make a compelling clinical case for utilizing RTU antibiotics, such as VANCO READY, to help reduce the potential for medication errors and improve patient safety. In addition, VANCO READY does not require thawing, compounding, or activating, and fits in automated dispensing cabinets.

Executive Summary: VANCO READY™ Premix Vancomycin Injection, USP Product Profiler *(cont)*

Why VANCO READY?

- VANCO READY offers a novel option that better adheres to emerging regulatory guidelines and accreditation requirements prioritizing premix antibiotics for managing sepsis and related high-risk infections, as supported by the American Society of Health-System Pharmacists (ASHP) and Institute of Safe Medication Practices (ISMP)[17,18]
- Prompt adoption of an IV premix vancomycin also has the potential to help
  - Reduce the potential for admixing errors[19,20]
  - Improve efficiency and patient safety in the ED and critical care unit (CCU)[21]
  - Improve adherence to medication management guidelines and standards[17,18,21]
  - Improve time-to-delivery of medications to patients with fewer labor handoffs or supply-chain delays[22,23]
  - Minimize drug waste/costs[22]

Safe Implementation Process Considerations

Due to the Boxed Warning for VANCO READY in pregnancy, hospitals/EDs and other institutions that may encounter patients of childbearing potential requiring treatment with vancomycin injection will need to employ a Safe Implementation Strategy. The following implementation strategy options are available for consideration by institutions:

1. Evaluate existing electronic health record and medication dispensing systems
2. Update EMR systems with appropriate safe dispensing protocols, including the use of automated dispensing cabinets (ADCs) and central pharmacy automation
3. Incorporate unique product barcodes in the EMR to support bedside barcode medication administration (BCMA), IV workflow system, and ADC system to guide dispensing and restocking
4. Develop educational plan for pharmacy and nursing staff

For more information on EMR best practices implementation, please visit www.xellia.com/us/products.

References: 1. VANCO READY (vancomycin injection, USP) [Prescribing Information]. Buffalo Grove: IL: Xellia Pharmaceuticals USA, LLC., 2019. **2.** Xellia Pharmaceuticals USA, LLC. Xellia Pharmaceuticals receives US FDA approval for premixed vancomycin injection. *Business Wire*. https://www.businesswire.com/news/home/20190219005196/en/Xellia-Pharmaceuticals-Receives-FDA-Approval-Premixed-Vancomycin. Published February 19, 2019. Accessed May 12, 2020. **3.** Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302(21):2323-2329. **4.** Liu V, Escobar GJ, Greene JD. Hospital deaths in patients with sepsis from 2 independent cohorts. *JAMA*. 2014;312(1):90-92. **5.** Healthcare Cost and Utilization Project (HCUP). HCUP Statistical Briefs - Costs & Charges. August 2019. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/reports/ statbriefs/sb_costs.jsp. Accessed May 12, 2020. **6.** Rhee C, Dantes R, Epstein L. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. *JAMA*. 2017;318(13):1241-1249. **7.** Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589-1596. **8.** Venkatesh AK, Slesinger T, Whittle J, et al. Preliminary performance on the new CMS Sepsis-1 National Quality Measure: Early insights from the Emergency Quality Network (E-QUAL). *Ann Emerg Med*. 2018;71(1):10-15.e1. **9.** Guilbart M, Zogheib E, Ntouba A, et al. Compliance with an empirical antimicrobial protocol improves the outcome of complicated intra-abdominal infections: a prospective observational study. *Br J Anaesth*. 2016;117(1):66-72. **10.** NORC at the University of Chicago. Recent Trends in Hospital Drug Spending and Manufacturer Shortages. Chicago, IL: NORC, January 15, 2019. https://www.aha.org/system/files/2019-01/aha-drugpricing-study-report-01152019.pdf. Accessed May 12, 2020. **11.** Eban K, Salzman S. In generic drug plants in China and India, data falsification is still a problem. October 29, 2019: *STAT News*. https://www.statnews.com/2019/10/29/data-falsification-still-problematic-china-indiageneric-drug-plants/. Accessed May 12, 2020. **12.** Weissman R. Hospitals struggle to obtain sterile water for injections, drugs. April 12, 2018: Supply Chain Dive. https://www.supplychaindive.com/news/hospitals-sterile-water-shortageinjections-drugs/521192/. Accessed May 12, 2020. **13.** Moresco BL, Woosley C, Sauter M, Bhalala U. Poor compliance with sepsis guidelines in a tertiary care children's hospital emergency room. *Front Pediatr*. 2018;6:53. **14.** Pacifica Compounding Pharmacy. 4 reasons why compounding medication take longer than regular prescriptions. http://www.pacificapharmacy.com/2016/02/17/4-reasons-why-compounded-medications-take-longer-than-regular-prescriptions/. Accessed May 12, 2020. **15.** Emerson BL, Ciaburri R, Brophy C, Kandil SB. Decreasing time to antibiotics for patients with sepsis in the emergency department. *Pediatr Qual Saf*. 2019;4(3):e173. **16.** Peltan ID, Brown SM, Bledsoe JR, et al. ED door-to-antibiotic time and long-term mortality in sepsis. Chest. 2019;155(5):938-946 **17.** Institute for Safe Medication Practices. ISMP guidelines for safe preparation of compounded sterile preparations. https://www.ismp.org/sites/default/files/attach¬ments/2017-11/Guidelines%20for%20Safe%20Preparation%20of%20Compounded%20Ster-ile%20Preperations_%20revised%202016.pdf. Updated 2016. Accessed May 12, 2020. **18.** Billstein-Leber M, Carrillo CJD, Cassano AT, Moline K, Robertson JJ. ASHP guidelines on preventing medication errors in hospitals. *Am J Health-Syst Pharm*. 2018;75(19):1493-1517. **19.** Flynn EA, Pearson RE, Barker KN. Observational study of accuracy in compounding iv admixtures at five hospitals. *Am J Health Syst Pharm*. 1997;54(8):904-912. **20.** Fanikos J. Premixed products improve safe medication practices. *Pharm Practice News*. 2011:56-57. https://mafiadoc.com/ premixed-products-improve-safe-medication-practices-pharmacy-_5a2dbcb01723dd05467ce637.html. Accessed May 12, 2020. **21.** Fanikos J. Reducing IV errors in the critical care setting. *Phar Purchasing Products*. 2012;(9):3;1. https://www.pppmag.com/ article/1080/march_2012_iv_safety/reducing_iv_errors_in_the_ critical_care_setting. Accessed May 12, 2020. **22.** Fanikos J, Erickson A, Munz KE, Sanborn MD, Ludwig BC, Van Hassel T. Observations on the use of ready-to-use and point-of-care activated products in automated dispensing cabinets in US hospitals. *Am J Health Syst Pharm*. 2007;64(19):2037-2043. **23.** D'Arrigo T. Pharmacists speed drug delivery in post-anesthesia care units. *Pharmacy Practice News*. 2010;37(6):4.

Please see full Prescribing Information for VANCO READY, including Boxed Warning, by visiting www.xellia.com/us/products.

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PRODUCT PROFILER

VANCO READY™
Premix Vancomycin Injection, USP

Contents

VANCO READY™
VANCOMYCIN injection, USP for intravenous use, Ready-to-Use (RTU)

US Food and Drug Administration-approved Indication:
Vancomycin Injection, USP is a glycopeptide antibacterial indicated in adult and pediatric patients (1 month and older) for the treatment of[1]:

- Septicemia
- Infective endocarditis
- Skin and skin structure infections
- Bone infections (osteomyelitis)
- Lower respiratory tract infections

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

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Please see additional Important Safety Information on page 34 and accompanying full Prescribing Information, including BOXED WARNING, for VANCO READY™ starting on page 35.

This publication is designed for payers, formulary committees, or other similar entities with knowledge and expertise in the area of healthcare economics making decisions regarding access, coverage, and reimbursement for VANCO READY™.

This publication was written by Jill Hughes and developed in collaboration with and with support from Xellia Pharmaceuticals USA, LLC.

Product Profiler

The Product Profiler publication provides pharmacy and therapeutics (P&T) committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler supplies information about pharmacology, clinical studies, FDA-approved indications, safety, efficacy, acquisition costs, and other pharmacoeconomic variables, along with additional P&T committee considerations, in a convenient package.

About the Author

Jill Hughes, MA, is a medical writer with over 2 decades of experience developing medical information content and pharmaceutical agent whitepaper summary publications across a variety of media and therapeutic areas. Her recent work has included developing accredited continuing medical education/continuing professional education (CME/CPE) content and executive whitepapers surrounding such diverse topics as pulmonary arterial hypertension; multidrug-resistant Gram-negative infections; invasive fungal infections; antimicrobial stewardship protocols; multiple sclerosis nursing policies and procedures; infusion safety and sterile-compounding safety in pharmacy practice; diabetes diagnosis and management; and HIPAA compliance, among other topics. Ms Hughes' other career highlights include developing patient-education television content for the Public Broadcasting System (PBS), partnering with organizations such as the American Medical Association (AMA) and the Institute for Safe Medication Practices (ISMP) on content/guideline development, and as a former in-house health policy analyst for the American Academy of Orthopedic Surgeons. Ms Hughes received her MA from the University of Chicago and her BA from the University of Cincinnati.

Disclosures

Xellia Pharmaceuticals USA, LLC provided funding for this publication. Jill Hughes reports she has no financial arrangement with Xellia Pharmaceuticals USA, LLC that might constitute a conflict of interest with respect to this publication.

Please see Important Safety Information on page 34 and accompanying full Prescribing Information, including BOXED WARNING, for VANCO READY™ starting on page 35.

Product Profiler

VANCO READY™
Premix Vancomycin Injection, USP

Contents

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Introduction

This Product Profiler introduces the healthcare professional to VANCO READY™, the first and only room temperature premix intravenous (IV) vancomycin agent currently available in the United States. VANCO READY™ is a novel premix ready to use (RTU) IV formulation of vancomycin, which received FDA approval for use in adults and children (1 month and older) on February 19, 2019.[2] In addition, this Profiler will examine clinical evidence surrounding the appropriate use of IV antibiotics on Gram-positive infections locally susceptible to vancomycin.

Sepsis is among the most expensive conditions treated in US hospitals and a leading cause of death, contributing to more than one-third of hospital deaths.[3-5] While some sepsis-related deaths are not preventable even with optimal care, sepsis-related mortality can be improved by optimizing antibiotic selection for all at-risk infections generally and by improving time-to-treat with effective antibiotics when patients present with identifiable symptoms of sepsis.[6-8]

Accordingly, in January 2020 the Centers for Medicare & Medicaid Services (CMS) released novel quality composite measures aimed at optimizing sepsis care in the United States in conjunction with its broader Surviving Sepsis Campaign. Selection and dispensing of appropriate antibiotics within a rapid timeframe is a key component of this measure set.[9] This Product Profiler introduces P&T committees and related healthcare stakeholders at local institutions to the latest clinical evidence surrounding the role of premix antibiotics in optimal clinical management of septicemia and other bacterial infections that pose a high risk of triggering septicemia.

Disease State Overview, Epidemiology, Related Cost Burden

Role of Vancomycin in Gram-Positive Infections

According to the *Extended Prevalence of Infection in Intensive Care (EPIC II)* study, Gram-positive bacterial infections represent a significant proportion (47%) of septicemia-related infections as well as other types of infections at high risk for triggering septicemia. A common site for infections is typically found in the respiratory tract. Study results indicated that 64% of infected patients had an infection in the lungs, followed by the abdomen (20%), the bloodstream (15%), and the renal tract/genitourinary system (14%).[10] Moreover, the majority of osteomyelitis (bone and joint infections)[11] and bacterial endocarditis[12] cases are caused by Gram-positive bacteria.

Vancomycin has been a key agent in the clinical armamentarium targeting Gram-positive infections for decades and is used frequently in all care settings where these infections are endemic. The World Health Organization (WHO) Model List of Essential Medicines, which has been published every 2 years since the late 1970s,[13,14] lists IV vancomycin as typically being used for any infection located outside the gut, due to low bioavailability of the oral dosage form of the compound.[15]

Clinical Uses of Vancomycin and Mechanism of Action Summary

Vancomycin is a tricyclic glycopeptide antibiotic derived from *Streptococcus orientalis*. Without factoring in local resistance trends, vancomycin typically has activity against the following species[15]:

- Streptococci
- Enterococci
- Methicillin-susceptible *Staphylococcus aureus* (MSSA)
- Methicillin-resistant *S aureus* (MRSA) strains

The mechanism of action of vancomycin involves inhibition of biosynthesis in Gram-positive bacterial cell walls.[16] The agent's biochemical process binds to D-alanyl D-alanine, which inhibits bacterial glucosyltransferase in target bacteria, resulting in cell destruction.[15] IV vancomycin is currently indicated for use against susceptible pathogens in the following infection categories[16]:

- Septicemia
- Infective endocarditis
- Skin and skin structure infections
- Bone infections
- Lower respiratory tract infections

Of note, vancomycin has no activity against Gram-negative bacteria or invasive fungal infections[16] (which may be comorbid with Gram-positive infections in select patients, such as those with compromised immune systems), so it should not be used

on a broad-spectrum basis. However, it may be paired with piperacillin/tazobactam or cefepime in select instances for broad-spectrum use, depending upon local susceptibilities, patient risk factors, and other local institutional preferences.[17-20] Prescribers and antimicrobial-stewardship personnel should remain up to date on local antibiograms across settings to determine levels of vancomycin resistance trends and appropriate coprescribing options for broad-spectrum use.

Burden of Disease for Vancomycin-Indicated Infections

The clinical and economic burden of disease for vancomycin-indicated infections is significant.

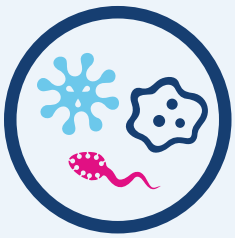
For example, there are over 1.7 million US cases of sepsis annually (inclusive of sepsis, severe sepsis, and septic shock), with 270,000 sepsis-related deaths annually. Of note, sepsis causes 1 in 5 (20%) of all deaths worldwide[21] and is a leading cause of death in US hospitals.[5] Annual costs of sepsis-related hospital admissions were estimated at $23.7 billion in 2013, making it among the top 4 costliest hospitalization conditions that year.[22]

Of note, while IV vancomycin is indicated for use in the treatment of septicemia, suboptimal management of the above-referenced localized infections can all subsequently trigger the development of septicemia.[16,23,24] **Therefore, it is reasonable to extrapolate that appropriate use of IV vancomycin in all indicated infections may subsequently help reduce morbidity and mortality associated with bacterial septicemia.**

Sepsis/septicemia/septic shock: 1.7 million annual US cases; 270,000 deaths annually. Sepsis is the cause of 1 in 5 deaths worldwide[21]

270,000 deaths annually

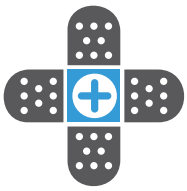
In 28% to 49% of sepsis cases, results are negative for culture,[25] plus the rapidly progressing condition means empirical treatment usually is required



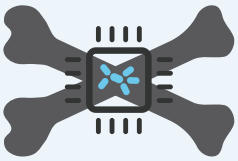
Lower respiratory tract infections (community-acquired): 1.08 million deaths in adults >70 years/2.38 million deaths in all age cohorts worldwide annually; *high risk of triggering sepsis*[26]

Infective endocarditis: 11.6 cases per 100,000 people in the United States, with 28% 5-year mortality[27,28]; cost burden of $2.34 billion in the United States in 2016[29]

Skin infections/structural tissue infections (SSTIs): 2.3 million cases in the United States occurred between 2005 and 2010, and over 4.8 million hospitalizations between 2005 and 2011.[30,31] Annual costs of SSTIs in 2012 were $15 billion[32]



Osteomyelitis (bone and joint infections): Osteomyelitis may be due to low vascularity of the bone tissue which makes it difficult to diagnose; these infections occur postoperatively in approximately 2% of hip and knee arthroplasties, with incidents rising annually[33,34]

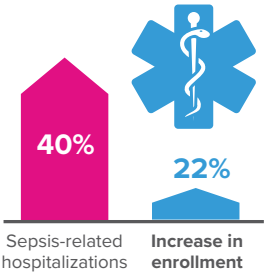


Cost of infected arthroplasty revisions: $320 million to $566 million annually.[34] Cases should be treated empirically, yet are best prevented via preoperative/perioperative prophylaxis with effective antibiotics[35-37]

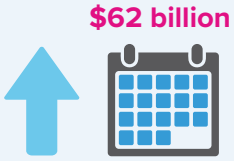
Economically speaking, data published by CMS in February 2020 as part of the largest ever study of Medicare sepsis data evaluated the increased rate of Medicare-enrolled patients hospitalized or housed within skilled nursing facilities (SNFs) with sepsis-related diagnoses between 2012 and 2018. After analyzing multiple epidemiological, economic, and morbidity/mortality trends and trajectories surrounding sepsis-related diagnoses in the Medicare population, the study concluded the following[38]:

Sepsis is increasing at nearly double the rate of rising Medicare enrollment,[38] likely reflecting a combination of suboptimal management of infections at risk for developing sepsis as well as the risk for sepsis in patients aged 65 and older

From 2012 to 2018, the **United States saw a 22% increase in Medicare enrollment, yet there was a 40% increase in the rate of sepsis-related hospitalizations among Medicare enrollees**[38]



Researchers projected that sepsis-related costs in 2019 could **reach more than $62 billion**[38]

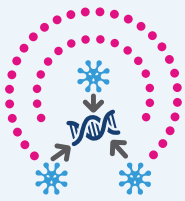


Estimated 6-month mortality of Medicare patients hospitalized or placed in SNFs with septic–shock-related diagnostic-related groups (DRGs) was **~60%**[39]

Patients with cancer, dementia, diabetes, and/or heart failure had an increased risk of dying following a sepsis diagnosis,[6] while hospital-acquired sepsis had higher mortality than community-acquired sepsis[39]

The single-year Medicare data for sepsis-related costs in **2018 (with a severe influenza season) was over $41.5 billion**[39]

Current trends of hypervirulent influenza and related viral infections (eg, COVID-19) appear to be contributing to increased recent comorbid bacterial pneumonia infections and related sepsis costs/mortality[39-41]

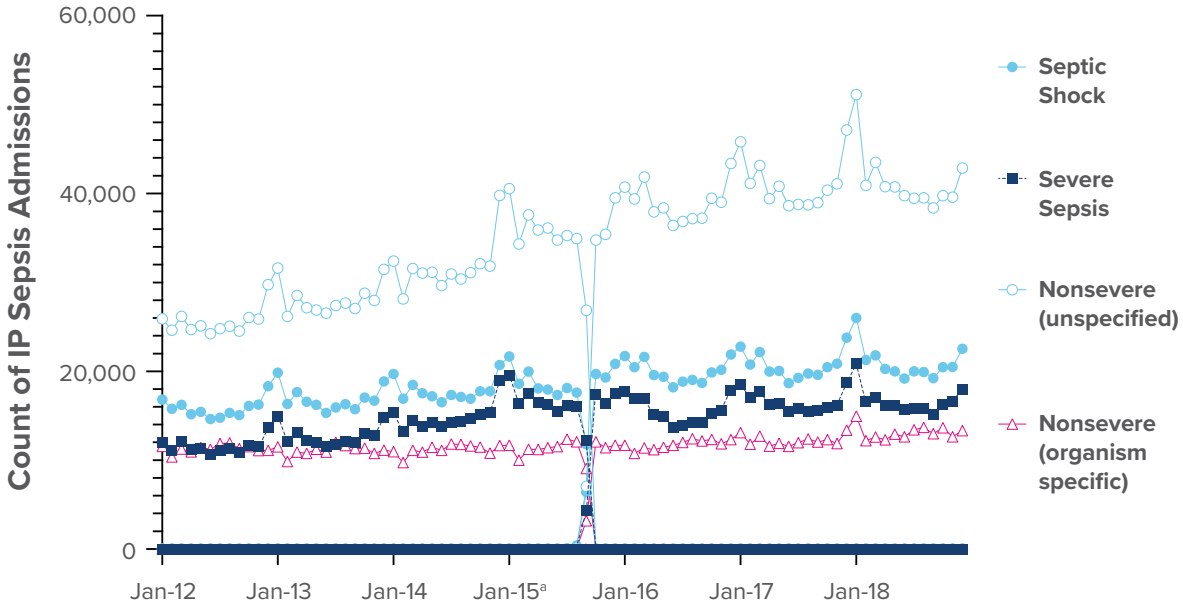


Conventional wisdom stipulates that milder sepsis cases that do not lead to septic shock have lower overall mortality. However, 2020 data from CMS indicate that this is not the case:

- Despite declining overall sepsis-related mortality during the 2012-2018 study period, **10% of Medicare patients with nonsevere forms of sepsis either died in the hospital or within 1 week of discharge**[38]
- **60% of patients** with nonsevere forms of sepsis **died within 3 years**[38]

Perhaps paradoxically, while septic shock is often viewed as more dangerous than sepsis or severe sepsis, it does not represent the highest proportion of inpatient admissions for sepsis **(Figure 1)**. These previously noted high all-cause mortality rates even among patients with nonsevere sepsis should alarm clinicians and place urgency on the re-evaluation of both inpatient and postdischarge sepsis care.

FIGURE 1. IP Sepsis Admissions, by Severity[39]



Analysis of sepsis admissions stratified by severity by counts, rates, and proportions (N=6,731,828 inpatient [IP] admissions to acute care hospitals of Medicare Part A/B beneficiaries).

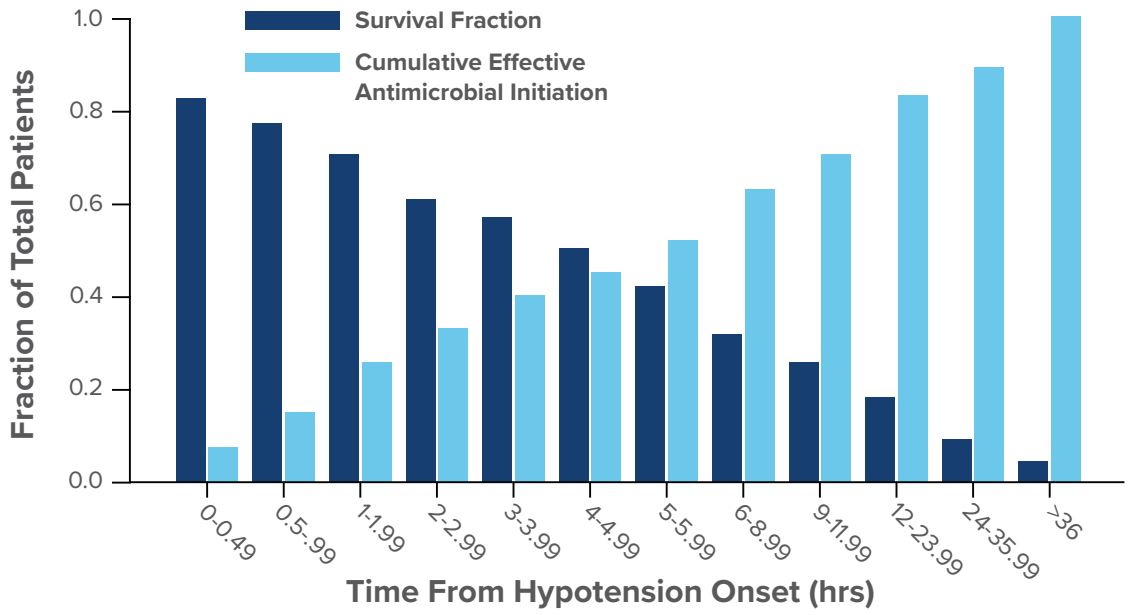
[a]In order to capture the maximum number of sepsis-associated inpatient admissions, the study used the SEP-1 denominator code set to identify, administratively, sepsis following the transition from ICD-9 to ICD-10 that occurred in October 2015.[39]

Source: Buchman TG et al. *Critical Care Medicine.* 2020;48(3):276-288.

Impact of Delayed Time-to-Treat in Sepsis Care

Multiple studies have found that suboptimal management of sepsis leads to increased mortality, especially when treatment with effective antibiotics is delayed in patients already demonstrating 1 or more sepsis-related symptoms. Two landmark studies (Peltan et al 2019; Kumar et al 2006) have determined that every 1-hour delay past a patient's arrival in the emergency department (ED) with sepsis increased the patient's odds of death. For example, Peltan et al found that the odds of 1-year mortality in treatment-delayed patients increases by 10% every hour, while Kumar et al found that every hour of treatment delay resulted in a mean 7.6% increase in mortality (range 3.6%-9.9%) (**Figure 2**).[42,43]

FIGURE 2. Duration of Hypotension Before Initiation of Effective Antimicrobial Therapy Is the Critical Determinant of Survival in Human Septic Shock[42]



Source: Kumar A et al. *Crit Care Med.* 2006;34:1589-1596.

Despite compelling data in favor of rapid time-to-treat with effective antibiotics in sepsis and septic shock, actual practice remains far behind the best clinical evidence. According to CMS data, only 57% of Medicare patients receive appropriate sepsis care—and clinical data are likely incomplete due to noninclusion of privately insured patients in currently available sepsis statistics.[44]

Further elucidating these data, the work of Levy et al on the Surviving Sepsis Campaign, an international guideline-based performance improvement study, found that **increased clinical compliance with evidence-based sepsis performance-measure bundles was associated with a 25% relative risk reduction in overall sepsis-related mortality, while every 10% increase in measure compliance was associated with a significant decrease in the odds ratio (OR) of hospital-related sepsis mortality.[45,46]**

Procedural/Operational Barriers to Optimal Treatment of Septicemia (All Causes)

While the myriad clinical data supporting the importance of rapid deployment of effective antibiotics in sepsis are well known, making optimal management of sepsis a reality in ground-level practice is far more complex to achieve. Multiple clinical, procedural, and operational aspects of ED care as well as community-based care can work together in concert to delay the timely treatment of sepsis. Moreover, suboptimal care of localized infections at high risk for triggering sepsis only exacerbates this trend.

Numerous procedural and operational barriers to delivering just-in-time effective antibiotics to patients with sepsis in the ED have been identified over the past decade. These include, but are not limited to:

- **Poor adherence to current sepsis diagnostic and antimicrobial treatment protocols**,[47] including poor clinical understanding of the sepsis immune response among ED personnel[48,49]
- **Lack of detailed bacterial culture isolates/local antibiogram data** for developing effective antimicrobial strategies for urgent treatment of sepsis and related antimicrobial stewardship, especially in community hospitals[50]
- **Increased bacterial resistance** to available antimicrobial agents and risk factors associated with some broad-spectrum agents (eg, renal failure), as well as local stewardship concerns about preventing the development of antimicrobial resistance to broad-spectrum agents[51,52]
- **Drug shortages,[53] supply-chain disruptions,[54] and quality control problems** due to manufacturing fraud or negligence,[55] and business-related factors (eg, cost). **Of note, 80% of US hospitals have reported difficulty obtaining essential medications.** Drugs impacted by medication shortages often include the sterile IV medications that are primarily used in the hospital setting.[53] Vancomycin is an example of an essential medication that has been impacted by these types of delay[56]
- **Shortage of qualified pharmacy technicians/pharmacists** for use in preparing and/or compounding of infusible antibiotics[57,58]
- **Lack of awareness or knowledge of sepsis identification and treatment preparation** by healthcare staff[49,59]
- **Overall clinical staff reductions, hospital budget cuts, hospital service cuts, and other administrative barriers** associated with rapidly rising drug costs and declining reimbursement[53]

Even when sepsis treatment protocols are followed consistently in US EDs, the lack of RTU infusible antibiotics with effective activity against likely infective organisms can contribute to treatment delays. **Moreover, hospitals that have not optimized dispensing of RTU antibiotics in the ED have reported effective antimicrobial treatment delays of up to 154 minutes (~2.5 hours)** from the time of patient arrival to the patient actually receiving the medication.[60] According to a 2019 study conducted in a US tertiary care pediatric hospital, removing procedural, logistical, and/or reconstituting/compounding-related barriers to dispensing effective antibiotics through changes in protocols, improved drug-stocking practices, and re-education of relevant clinical staff resulted in a significant reduction in treatment delays.[60]

Clinical Risks of Locally Compounded Antimicrobials in Lieu of Mass-Manufactured Agents

When a drug shortage or cost-cutting measures make a desired medication unavailable, hospitals may turn to compounding. Errors can result due to a lack of training or unfamiliarity with the compounded medications and have resulted in increased safety risk to patients as well as increased legal risks for healthcare providers and organizations.[61,62]

Indeed, **up to 33% of locally compounded drugs (all routes of administration) tested for adherence to United States Pharmacopeia (USP)/FDA quality standards (eg, potency, contamination, uniformity) failed FDA testing, with incorrect potency versus standard labeling the most common deficiency**. Potency testing failures in sampled compounded drugs ranged from 68% to 268% of the labeled dosage,[63] which in infusible antibiotics could potentially contribute to undertreatment of sepsis infections, overdosage resulting in toxicity-related harm, and/or the development of increased antimicrobial resistance.[64]

Another study that solely examined IV admixtures via observational analysis of 5 hospital pharmacies conducting local compounding of IV drugs detected an error rate of 9% (145 errors for 1679 doses), excluding RTU products, with wrong-dose errors constituting the most common type of error.[65]

Most patients presenting in the ED with sepsis symptoms eventually end up on a hospital's critical care unit (CCU), and two-thirds of critical-care patients will require at least one IV-administered drug. Accordingly, critical-care patients are at higher risk for medication errors than non–critical-care patients, due to increased incidence of IV push-related errors versus other routes of administration; moreover, the most likely source of medication errors in the CCU is at the drug-preparation level.[66] A significant proportion of dispensing-related pharmacy errors also go undetected.[67]

In one study, up to two-thirds of IV drug infusions prepared by nurses in the CCU did not match clinical or quality standards or even physicians' dosing orders,[68] while transcription-related medication errors (eg, transposing "mcg" with "mg"); misinterpretation of physicians' orders or patient notes; errors of omission (eg, drug ordered but patient did not receive or patient was not prescribed necessary medications); and general human/analytical error are all common in the hectic CCU.[69,70]

Costs/Risks of Nonadherence to ASHP and ISMP Guidelines for IV Therapy/Compounded Therapies ("Use Most Ready-To-Use Formulation")

Regulators and accrediting bodies have noted the high error rates associated with local compounding and in recent years have taken steps to discourage the practice. Even hospitals that outsource compounding to an accredited (eg, 503b) outside service face increased regulatory scrutiny, and cost should not be the only determining factor in deciding to compound locally or via outsourcing.[71]

Indeed, USP <797> regulations launched in 2008 stipulate criteria that compounding pharmacies operating under the 503b umbrella should adhere to. Despite this guidance, compliance was an issue and a number of incidents with contaminated compounded products led to additional regulations in 2013 in the form of the Drug Quality and Security Act. This law further defined expectations for 503b pharmacies, which include outsourcing facilities that may distribute compounded drugs either pursuant to a patient-specific prescription or in response to an order from a hospital.[72,73]

Numerous incidences of patient harm/mortality related to contaminated or otherwise substandard compounded products mean that hospitals that choose to compound locally or even outsource compounding instead of using ready-made products expose their organizations and patients to unnecessary risk and related liability.[74] Indeed, if an FDA-approved drug is commercially available and patient needs (eg, allergy to manufactured drug components or other contraindication) do not require the use of a compounded product, the use of a locally compounded product that is not FDA approved and subject to Good Manufacturing Practice (GMP) confers additional risk with no or negative additional benefits.[64]

Accordingly, the FDA has taken a rather hard line against the use of locally compounded products when mass-produced options are available, and regulators/accreditors are following suit. In 2012, following a series of incidents in which locally compounded versions of drugs such as hydroxyprogesterone caproate were found to have unacceptable levels of impurities/adulterations as well as nonstandard potency, the **FDA issued a statement that if an FDA-approved manufactured drug is available and safe for a patient, it should be prescribed and used. Moreover, the FDA emphasized that compounding large volumes of copies of approved drugs does not fall within the traditional scope of pharmacy practice, and may in turn be subject to civil and/or criminal penalties.**[75] Therefore physicians, pharmacists, and/or hospitals who prescribe or dispense compounded drugs without holding additional malpractice liability coverage for compounding may find themselves financially unprotected in the event of a lawsuit due to patient harm caused by faulty compounded medications.[76-78]

As a direct result of the FDA tightening its own regulations and enforcement since 2012 and ongoing, clinical practice guidelines and accreditation standards published between 2014 and 2018 by the Institute of Safe Medication Practices (ISMP), the American Society of Health-System Pharmacists (ASHP), and The Joint Commission have all prioritized the use of commercially prepared, RTU infusible products in standardized dosages to reduce the potential of medication errors. A summary of the standards follows:

"To the maximum extent possible, commercially-prepared, premixed parenteral products and unit dose syringes are used versus manually compounded sterile products."—*ISMP*[79]

"Whenever possible, medications should be available for inpatient use in unit-of-use and ready-to-administer packaging without further manipulation by the person administering the medication."—*ASHP*[80]

"Medications in patient care areas are available in the most ready-to-administer forms commercially available or, if feasible, in unit doses that have been repackaged by the pharmacy or a licensed repackager. Note: This element of performance is also applicable to sample medications."
—*Joint Commission Medication Management Standards*[81]

As noted, FDA regulations require that any facility doing large-scale compounding receive federal 503b designation. Facilities that operate outside of 503b regulations may face federal penalties, including FDA warning letters, fines, drug recalls, and other penalties.

Between 2013 and 2017, the FDA issued hundreds of warning letters and recalls of compounded drugs.[82]

Penalties for noncompliance with these medication management standards may include:

Fines/other financial penalties[83]

Reimbursement penalties (including nonreimbursement of services)[83]

Civil/criminal liability, up to and including felonies[84]

Loss of hospital and/or pharmacy accreditation status[84,85]

Given significant risks of error and patient harm associated with IV drug delivery systems generally, and locally compounded drugs specifically, the Second Consensus Development Conference on the Safety of Intravenous Drug Delivery Systems[86] and the ASHP have developed recommendations for hospitals and other institutions to minimize these risks of harm, medication errors, contamination, and/or overdose. **In these compiled recommendations, point-of-care activated, non-compounded/non-reconstituted, manufacturer RTU agents with the longest possible expiration date available are prioritized to help minimize costs and waste associated with short shelf life/spoilage.[86,87] (Tables 1 and 2)**

TABLE 1. Common Issues Associated With IV Drug Delivery Systems[86]

Product Type	Benefits	Problems
Non–pharmacy-compounded at point of care	Can customize dose for each patient, immediate availability	High potential for error, low compliance with regulatory requirements, labeling typically handwritten or absent, risk for contamination
Pharmacy-compounded	Can customize dose for each patient, significant quality control, labeled in accordance with hospital standards	Risk for contamination, significant operational requirements related to USP Chapter <797>
Point-of-care activated	Works well with automated cabinets, longest expiration date	Products not available for special patient populations, cost analysis recommended, risk for inactivation errors
Outsourced RTU	Can customize dose for each patient, low risk for contamination	Cost analysis recommended, requires advanced planning and storage
Manufacturer RTU	Low risk for contamination, ease of use and dispensing, longest expiration date	Products not available for special patient populations, lack of pharmacoeconomic data, frozen products require thawing

Adapted from the Second Consensus Development Conference on the Safety of Intravenous Drug Delivery Systems.

TABLE 2. Summary of the ASHP Statement on the Role of the Pharmacist in the Selection of IV Drug Delivery Systems[87]

Evaluate and research the direct and comparative efficacy, safety, and cost-effectiveness of specific drug delivery systems and administration devices.
Work with all appropriate medical and administrative staff on the selection or exclusion of particular drug delivery systems and administration devices for use in specific organizational settings.
Assist in the development of organization-specific policies and procedures regarding the acquisition, storage, distribution, use, maintenance, and ongoing product quality control of drug delivery systems and administration devices.
Assist in the selection of a particular drug delivery system and administration devices for use in specific patients' drug therapy.
Instruct patients on the use of such systems and devices to gather information necessary to monitor the outcome of their therapy.
Monitor the clinical effectiveness and suitability of drug delivery systems and administration devices with respect to specific patients and communicate clinically relevant observations and recommendations to prescribers and other health professionals involved in the patients' care.

In addition to clinical concerns regarding poor efficacy, dosing errors, and antimicrobial contamination, there are increased costs/waste associated with in-OR perioperative compounding of IV antimicrobials such as vancomycin. While the current and immediately past USP <797> standards for Beyond Use date (BUD) of sterile compounded vancomycin are both technically permissible under Joint Commission requirements as of March 2020, the shelf life of compounded sterile IV vancomycin prepared in a non–clean-room setting (Category 1) is generally accepted at ≤12 hours once it is administered to a patient due to sterility loss and possible drug spoilage. **Compounding in the OR setting is automatically considered Category 1, the shortest duration BUD standard because it is conducted outside the clean-room/hood setting (Table 3).**[88,89]

TABLE 3. Sterile Compounded IV Vancomycin Beyond-Use Dating (BUD):

Comparison of ASHP Extended Stability[a] and USP <797> Standards
- Product gets shorter of the 2 dates under room temp/refrigerated conditions
- Standard comparison for Compounded Sterile Products (CSPs) in PVC Bags

ASHP Standard (ASHP Extended Stability Book) for Vancomycin in PVC Bags[89,b]:

- 17 days room temperature, 58 days refrigerated

USP Compounding Standards and Beyond-Use Dates (BUDs)[88]:

The table below summarizes and compares the storage periods and the BUDs in the official chapter and the revised chapter.
- Pharmacies can choose to comply with 2008 or 2019 guidelines in their entirety

Guidelines	
Official (last revised in 2008)	***Revised*** (June 2019)
Low risk in segregated compounded area • 12 hours at controlled room temperature (CRT) **Low risk** • 48 hours at CRT • 14 days in a refrigerator • 45 days in a freezer **Medium risk** • 30 hours at CRT • 9 days in a refrigerator • 45 days in a freezer **High risk** • 24 hours at CRT • 3 days in a refrigerator • 45 days frozen	**Category 1** • ≤12 hours at CRT • ≤24 hours in a refrigerator **Category 2**[c] • 4 days at CRT • 10 days in a refrigerator • 45 days in a freezer

[a] Of note, ASHP standard is longer than USP BUD regulations, so USP <797> are preferred compared to the ASHP Stability Info unless sterility testing is completed (usually conducted only in 503b setting).
[b] The new ASHP guidelines are not yet in effect, but facilities can choose to comply with the new guidelines per Joint Commission.
[c] The USP defines these selected storage options for aseptically processed CSPs without sterility testing, compounded from sterile starting ingredients.

BUD standards under ASHP or USP guidelines may render the product spoiled for sterile OR use quickly,[88,89] and valuable OR time is also spent compounding sterile medications instead of on actual surgery, leading to inefficiencies. Most institutions are under pressure to increase efficiency in the valuable OR setting, and **with the cost of care in the OR averaging $36 to $37 per minute, any efficient use of resources would be beneficial. The Joint Commission, ASHP, and ISMP, along with other organizations, recommend using RTU IV push medications to avoid the unnecessary complexity of preparing and administering parenteral IV push medications.**[90,91]

Advantages (Operation, Cost, Safety) of Using Premix Antibiotics

As noted previously, ISMP/ASHP/Joint Commission guidelines and other consensus recommendations on IV drug safety increasingly implore hospitals to use the "Most Ready-To-Use Formulation" of drugs, mass-produced according to GMP generally, and specifically, manufacturer RTU IV formulations that may be automatically dispensed/require no additional administrative manipulation from nursing staff.

Waste, Labor Overspend, and Related Financial/Operational Loss Associated With Compounded and Short-Dated IV Medications

It is estimated that **billions of dollars worth of drugs are discarded** by healthcare organizations such as hospitals, retail pharmacies, and nursing homes annually.[92]

When narrowed down to the per-hospital drug-waste spend on IV-based therapies only, **1 US hospital (Allegheny General Hospital, Pittsburgh, PA) determined it wasted 33,215 IV bags annually, at a cost of $391,753 annually, due to short-dating.**[93]

Shortages of pharmacy technicians[57] **and certification requirements**[94] for sterile compounding make labor costs associated with compounding unsupportable when a safe admix option is available.

Regulators (FDA, Joint Commission, ASHP, USP) are cracking down against the routine use of compounded medications.[95]

Thanks in part to the reduction of required administrative handoffs/transport steps as well as the elimination of local compounding-related contamination, a 2013 study demonstrated that premixed antibiotics show reduced time to first dose for patients with sepsis in the ED setting versus non-premixed antibiotics. A retrospective study of an ED with a Level I trauma center and annual census of 70,000 patients found that premixed antibiotics were used 55% of the time in patients with sepsis presenting in its ED; in these patients, the time to administration of the initial antimicrobial agent was significantly improved, to less than 1 hour (~50 minutes).[96]

This improvement was the first that scientifically observed and tracked statistical improvement in time-to-treat with effective antibiotics in accordance with the US Surviving Sepsis Campaign recommendations, which include the recommended storage of premix, automatically dispensed antimicrobials right in the ED to reduce time-to-treat with effective antibiotics of patients presenting with recognizable sepsis symptoms.[97]

For the purposes of the Kufel et al study, premix antibiotics were defined as meeting the following criteria[96]:

1. Stored in an ED automated dispensing cabinet (ADC)

2. Provided in a shelf-stable preparation that did not require reconstitution and/or dilution prior to administration

Time to administration of the initial antimicrobial agent was significantly improved **to less than 1 hour (~50 minutes)**.[96]

Clinical Product Information/Indications

Premix vancomycin (VANCO READY™) is a novel formulation of the existing antimicrobial vancomycin. Unlike legacy formulations that require refrigeration and/or reconstitution, as well as patient-level dosing prep which may lead to overdose/underdose or other product consistency issues, this novel, single-dose formulation includes stabilizers that allow the product to be stored safely at room temperate (up to 25°C) for 16 months. The product should be used within 28 days of removal from aluminum overpouch.[1] Multiple single-dose bags, including:

- 500 mg/100 mL
- 750 mg/150 mL
- 1 g/200 mL
- 1.25 g/250 mL
- 1.5 g/300 mL
- 1.75 g/350 mL
- 2 g/400 mL

No vials, adapters, or other extra administrative paraphernalia are necessary for use with VANCO READY™. This product also fits in most commercially available ADCs. Because it requires no compounding, no reconstitution, no local dose mixing, and can be dispensed in the ED, no institutional 503b certification(s) are required to stock or dispense this product, which is becoming of increased concern given stricter FDA interpretation of the 503b standard and related enforcement.

Due to the novel excipients in VANCO READY™, it should not be administered to women who are or may be pregnant. If therapy with vancomycin is needed during pregnancy, use other available formulations of vancomycin. Please see additional information on safety considerations and pregnancy use on **page 21** in this profiler, and the accompanying full Prescribing Information starting on **page 35** for more information.

As with existing formulations of vancomycin, the FDA has approved clinical use of premix IV vancomycin (VANCO READY™) for 5 main subsets of infectious disease[1]:

- Septicemia (All Causes w/Gram-positive bacteria)
- Bacterial lower respiratory tract infections (eg, MRSA pneumonia, other community-acquired pneumonia from Gram-positive bacteria)
- Infective endocarditis
- SSTIs (eg, cellulitis, surgical site infections)
- Osteomyelitis (eg, postarthroplasty infections, other bone infections)

Chemistry, Clinical Pharmacology, Other Details

Vancomycin HCl Injection, USP
For Intravenous Use Only

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.[1]

Vancomycin Injection, USP, in single-dose flexible bags contain vancomycin as vancomycin hydrochloride. It is a tricyclic glycopeptide antibacterial drug derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*).[1]

Vancomycin Injection, USP, in single-dose flexible bags are sterile, nonpyrogenic premixed 100 mL, 150 mL, 200 mL, 250 mL, 300 mL, 350 mL, or 400 mL solution containing 500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g, or 2 g vancomycin, respectively, as vancomycin hydrochloride. Each 100 mL of solution contains 1.8 mL polyethylene glycol 400, 1.36 g N-acetyl-D-alanine, 1.26 g L-lysine hydrochloride (monochloride) in water for injection. Hydrochloric acid and sodium hydroxide are used for pH adjustment. The pH is 4.5 to 5.5 and the osmolarity is 350 to 475 mOsmol/L.[1]

CLINICAL PHARMACOLOGY[1]

Pharmacodynamics

The pharmacodynamics of vancomycin is unknown.

Pharmacokinetics

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 like those after a single dose.

Distribution

The volume of distribution ranges from 0.3 to 0.43 L/kg after intravenous administration.

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.

Elimination

Mean plasma clearance is about 0.058 L/kg/h, and mean renal clearance is about 0.048 L/kg/h. The mean elimination half-life of vancomycin from plasma is 4 to 6 hours in subjects with normal renal function. In anephric patients, the mean elimination half-life is 7.5 days. Total body and renal clearance of vancomycin may be reduced in the elderly.

Metabolism

There is no apparent metabolism of the vancomycin.

Excretion

In the first 24 hours after intravenous administration, about 75% of an administered dose of vancomycin is excreted in urine by glomerular filtration. Renal impairment slows excretion of vancomycin.

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.

Microbiology

Mechanism of Action

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

Resistance

Vancomycin is not active *in vitro* against Gram-negative bacilli, mycobacteria, or fungi. There is no cross-resistance between vancomycin and other antibacterials.

Interaction with Other Antimicrobials

The combination of vancomycin and an aminoglycoside acts synergistically *in vitro* against many isolates of *Staphylococcus aureus*, *Streptococcus gallolyticus* (previously known as *Streptococcus bovis*), *Enterococcus* spp, and the viridans group streptococci.

Antimicrobial Activity

Vancomycin has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections:

Aerobic Gram-Positive Bacteria

- *Corynebacterium* spp.
- *Enterococcus* spp. (including *Enterococcus faecalis*)
- *Staphylococcus aureus* (including methicillin-resistant and methicillin-susceptible isolates)
- Coagulase negative staphylococci (including *S. epidermidis* and methicillin-resistant isolates)
- *Streptococcus gallolyticus* (previously known as *Streptococcus bovis*)
- Viridans group streptococci

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

At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for vancomycin against isolates of similar genus or organism group. However, the efficacy of vancomycin in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Bacteria

- *Listeria monocytogenes*
- *Streptococcus pyogenes*
- *Streptococcus pneumoniae*
- *Streptococcus agalactiae*

Anaerobic Gram-Positive Bacteria

- *Actinomyces* species
- *Lactobacillus* species

Susceptibility Testing[1]

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

Dosage and Administration[1]

Important Administration Instructions

Use this formulation of Vancomycin Injection, USP only in patients who require the entire (500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g, or 2 g) dose and not any fraction thereof.

Vancomycin Injection, USP in transparent single-dose flexible bags are intended for intravenous use only. Do **NOT** administer orally.

To reduce the risk of infusion related adverse reactions, administer Vancomycin Injection, USP by intravenous infusion over 60 minutes or greater. An infusion rate of 10 mg/min or less is associated with fewer infusion-related events. Infusion related events may occur, however, at any rate or concentration.

Drug additives should not be made to this solution.

Vancomycin Injection, USP concentrations of no more than 5 mg/mL are recommended in adults. See also age-specific recommendations.

Administer Vancomycin Injection, USP prior to intravenous anesthetic agents to reduce the risk of infusion related adverse reactions.

Administer Vancomycin Injection, USP by a secure intravenous route of administration to avoid local irritation and phlebitis reactions.

Dosage in Adult Patients with Normal Renal Function

The usual daily intravenous dose is 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours. Administer each dose by intravenous infusion over a period of 60 minutes or greater. Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose. The initial daily dose should be no less than 15 mg/kg.

Dosage in Pediatric Patients (1 Month and Older) with Normal Renal Function

Use this formulation of Vancomycin Injection, USP only in pediatric patients (1 month and older) who require the entire dose (500 mg, 750 mg, 1 g, 1.25 g, 1.5g, 1.75 g, 2 g) of this single-dose flexible bag and not any fraction of it.

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.

Dosage in Patients with Renal Impairment

Dosage adjustment must be made in patients with renal impairment. The initial dose should be no less than 15 mg/kg in patients with any degree of renal impairment.

In the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Measure trough vancomycin serum concentrations to guide therapy, especially in seriously ill patients with changing renal function.

For functionally anephric patients, an initial dose of 15 mg/kg of body weight should be given to achieve prompt therapeutic serum concentration. A dose of 1.9 mg/kg/24 h should be given after the initial dose of 15 mg/kg.

Directions for Use of Vancomycin Injection, USP and Storage Instructions

Vancomycin Injection, USP, in transparent single-dose flexible bag is for intravenous administration only.

Vancomycin Injection, USP is room temperature stable, ready-to-use drug product.

Preparation for Intravenous Administration:

1. Remove the flexible bag from aluminum overpouch.
2. Check for minute leaks by squeezing the bag firmly. If leaks are detected, discard solution because sterility may be impaired. Leaks may be more readily detected by wrapping the bag with blotting paper or a tissue before squeezing.
3. Do not add supplemental medication.
4. Visually inspect the flexible bag. If the outlet port protector is damaged, detached, or not present, discard the flexible bag as solution path sterility may be impaired. If after visual inspection the solution is cloudy or if an insoluble precipitate is noted or if any seals are not intact, the flexible bag should be discarded.
5. The solution in the flexible bag remains chemically stable for 28 days at room temperature (up to 25°C/77°F) after removal from the aluminum overpouch. Discard unused drug.
6. Suspend the flexible bag from eyelet support.
7. Remove protector from outlet port at bottom of flexible bag.
8. Attach administration set. Refer to complete directions accompanying set.
9. Use sterile equipment.

Do **NOT** use flexible bags in series connections. Such use could result in an embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

CONTRAINDICATIONS[1]

Vancomycin Injection, USP is contraindicated in patients with known hypersensitivity to vancomycin.

STORAGE[1]

VANCO READY™ is room temperature, no refrigeration/reconstituting are required for this formulation. Store at room temperature, below 25°C (77°F) in original packaging.

Clinical Data

Clinical Trials Experience[1]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following adverse reactions associated with the use of vancomycin were identified in clinical trials:

Immune system disorders: Hypersensitivity reactions including anaphylaxis and "red man syndrome"

Skin and subcutaneous tissue disorders: Erythema (especially of the face, neck and upper torso) and pruritus which are manifestations of rashes including exfoliative dermatitis, linear IgA bullous dermatosis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Renal and urinary disorders: Acute kidney injury and interstitial nephritis

Ear and Labyrinth Disorders: Tinnitus, hearing loss, vertigo

Blood and Lymphatic System Disorders: Agranulocytosis, neutropenia, pancytopenia, leukopenia, thrombocytopenia, eosinophilia

Gastrointestinal Disorders: Pseudomembranous colitis

Cardiac Disorders: Cardiac arrest, chest pain

General Disorders and Administration Site Conditions: General discomfort, fever, chills, phlebitis, injection site irritation, injection site pain and necrosis following intramuscular injection, chemical peritonitis following intraperitoneal administration (Vancomycin Injection, USP is not approved for intramuscular and intraperitoneal administration)

Laboratory Abnormalities: Elevated blood urea nitrogen, elevated serum creatinine

Musculoskeletal and connective tissue disorders: Muscle pain

Nervous system disorders: Dizziness

Respiratory, thoracic and mediastinal disorders: Wheezing, dyspnea

Vascular disorders: Hypotension, shock, vasculitis

Postmarketing Experience[1]

The following adverse reactions have been identified during postmarketing 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)

Areas of Future Postmarketing Study:

The manufacturer (Xellia Pharmaceuticals USA, LLC) is currently conducting postmarket studies on the following investigative topics related to VANCO READY™:

- Safety/efficacy of the co-administration of Vancomycin Injection USP and piperacillin tazobactam.
- Safety/efficacy of the co-administration of Vancomycin Injection USP and cefepime.

Safety Considerations

USE IN SPECIFIC POPULATIONS[1]

Pregnancy

Risk Summary

This formulation of Vancomycin Injection, USP is not recommended for use during pregnancy because it contains the excipients, PEG 400 and NADA, which caused fetal malformations in animal reproduction studies. Advise pregnant women of the potential risk to the fetus. If therapy with vancomycin is needed during pregnancy, use other available formulations of vancomycin.

There are no available data on vancomycin use in pregnant women to inform a drug-associated risk of major birth defects or miscarriage. Available published data on vancomycin use in pregnancy during the second and third trimesters have not shown an association with adverse pregnancy related outcomes. There are no available data on first trimester use of vancomycin, including vancomycin with the excipients PEG 400 and NADA, in pregnant women to assess the risk of major birth defects or miscarriage. Vancomycin alone did not show adverse developmental effects when administered intravenously to pregnant rats and rabbits during organogenesis at doses less than or equal to the recommended maximum human dose based on body surface area.

Reproduction studies in rabbits with intravenous doses of PEG 400 at approximately 5 times the maximum daily human dose based on body surface area comparisons administered during organogenesis resulted in fetal spinal malformations. Reproduction studies in rabbits and rats using intravenous doses of NADA at approximately 6 and 7 times the maximum daily human dose, respectively, based on body surface comparisons resulted in maternal toxicity and fetal spinal and cardiovascular malformations in rabbits, and maternal toxicity with no significant adverse embryo-fetal effects in rats. Vancomycin alone did not show adverse developmental effects when administered intravenously to pregnant rats and rabbits during organogenesis at doses less than or equal to the recommended maximum human dose based on body surface area.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

There are no available data on first trimester use of vancomycin, including vancomycin with the excipients PEG 400 and NADA, in pregnant women to assess a risk of major birth defects or miscarriage.

A published study evaluated hearing loss and nephrotoxicity in infants of 10 pregnant intravenous drug users treated with vancomycin (formulation did not include the excipients PEG 400 and NADA) for suspected or documented methicillin-resistant *Staphylococcus aureus* in the second or third trimester. The comparison groups were 10 uninfected non-intravenous drug-dependent patients, and 10 uninfected intravenous drug-dependent patients who served as substance abuse controls. No infant in the vancomycin exposed group had abnormal sensorineural hearing at 3 months of age or nephrotoxicity.

A published prospective study assessed outcomes in 55 pregnant women with a positive Group B streptococcus (GBS) culture and a high-risk penicillin allergy with resistance to clindamycin or unknown sensitivity who were administered vancomycin (formulation did not include the excipients PEG 400 and NADA) at the time of delivery. Vancomycin dosing ranged from the standard 1 g intravenously every 12 hours to 20 mg/kg intravenous every 8 hours (maximum individual dose 2 g). No major adverse reactions were recorded either in the mothers or their newborns. None of the newborns had sensorineural hearing loss. Neonatal renal function was not examined, but all of the newborns were discharged in good condition.

Animal Data

Vancomycin did not cause fetal malformations when administered during organogenesis to pregnant rats (gestation days 6 to 15) and rabbits (gestation days 6 to 18) at the equivalent recommended maximum human dose (based on body surface area comparisons) of 200 mg/kg/day IV to rats or 120 mg/kg/day IV to rabbits. No effects on fetal weight or development were seen in rats at the highest dose tested or in rabbits given 80 mg/kg/day (approximately 1 and 0.8 times the recommended maximum human dose based on body surface area, respectively). Maternal toxicity was observed in rats (at doses 120 mg/kg and above) and rabbits (at 80 mg/kg and above).

Animal reproduction studies conducted in rabbits administered intravenous PEG 400 at 2000 mg/kg (approximately 5 times the maximum daily human dose, based on body surface comparisons) during organogenesis (gestation days 6 to 19) resulted in fetal scoliosis (thoracic and lumbar) and increased

incidence of delayed or incomplete ossification of the pubes, epiphyses, and talus bones. No maternal toxicity was observed up to the maximum dose tested.

Similarly, in animal reproduction studies conducted in pregnant rabbits (gestation days 6 to 19) and pregnant rats (gestation days 6 to 17) administered intravenous NADA at 1680 and 3780 mg/kg, respectively (approximately 6 and 7 times the maximum daily human dose, respectively, based on body surface area comparisons) resulted in fetal scoliosis and a spectrum of rare cardiovascular anomalies in rabbits and no adverse effects on fetuses in rats. Increased incidence of delayed or incomplete ossifications of the metacarpals/metatarsals/phalanges and increased ossification (fused jugal/maxilla bones) were observed in rabbits at 1680 mg/kg. Minor fetal skeletal abnormalities were observed in rats at 3780 mg/kg which was also associated with maternal toxicity including increased incidence of litter loss.

No animal studies have been conducted to evaluate the potential reproductive and embryo-fetal effects of Vancomycin Injection, USP.

Lactation

Risk Summary

There are insufficient data to inform the levels of vancomycin in human milk. There are no data on the effects of vancomycin on the breastfed infant or milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for vancomycin and any potential adverse effects on the breastfed infant from vancomycin or from the underlying maternal condition.

Females and Males of Reproductive Potential

Pregnancy Testing

Perform a pregnancy test in females of reproductive potential prior to prescribing this formulation of vancomycin.

Pediatric Use

Vancomycin Injection, USP is indicated in pediatric patients (1 month and older). In pediatric patients, monitor vancomycin serum concentration and renal function when administering Vancomycin Injection, USP. More severe infusion related reactions related to vancomycin administration may occur in pediatric patients. Concomitant administration of vancomycin and intravenous anesthetic agents has been associated with erythema and histamine-like flushing in all patients including pediatric patients.

Geriatric Use

Vancomycin is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Warnings and Precautions[1]

Risk of Embryo-Fetal Toxicity Due to PEG 400 and NADA Excipients

This formulation of Vancomycin Injection, USP is not recommended during pregnancy because it contains the excipients PEG 400 and NADA, which caused fetal malformations in animal reproduction studies. The active ingredient vancomycin is not known to be associated with embryo-fetal toxicity.

Advise pregnant women of the potential risk to the fetus. If use of vancomycin is needed during pregnancy, use other available formulations of vancomycin.

Infusion Reactions

Hypotension, including shock and cardiac arrest, wheezing, dyspnea, urticaria, muscular and chest pain may occur with rapid Vancomycin Injection, USP administration. The reactions may be more severe in younger patients, particularly children, and in patients receiving concomitant muscle relaxant anesthetics.

Rapid intravenous administration of Vancomycin Injection, USP may also be associated with "red man syndrome", which manifests as pruritus and erythema that involves the face, neck and upper torso.

Infusion-related adverse reactions are related to both the concentration and the rate of administration of vancomycin. Infusion-related adverse reactions may occur, however, at any rate or concentration.

Administer Vancomycin Injection, USP over a period of 60 minutes or greater to reduce the risk of infusion-related adverse reactions. 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 adverse reactions. Administer prior to intravenous anesthetic agents when feasible. Stop the infusion if a reaction occurs.

Nephrotoxicity

Vancomycin Injection, USP can result in acute kidney injury (AKI), including acute renal failure, mainly due to interstitial nephritis or less commonly acute tubular necrosis. AKI is manifested by increasing blood urea nitrogen (BUN) and serum creatinine (Cr). The risk of AKI increases with higher vancomycin serum levels, prolonged exposure, concomitant administration of other nephrotoxic drugs, concomitant administration of piperacillin-tazobactam, volume depletion, pre-existing renal impairment and in critically ill patients and patients with co-morbid conditions that predispose to renal impairment.

Monitor serum vancomycin concentrations and renal function in all patients receiving Vancomycin Injection, USP. More frequent monitoring is recommended in patients with comorbidities that predispose to impairment in renal function or are concomitantly receiving other nephrotoxic drugs, in critically ill patients, in patients with changing renal function, and in patients requiring higher therapeutic vancomycin levels. If acute kidney injury occurs, discontinue Vancomycin Injection, USP or reduce the dose.

Ototoxicity

Ototoxicity has occurred in patients receiving vancomycin. It may be transient or permanent. Ototoxicity manifests as tinnitus, hearing loss, dizziness or vertigo. The risk is higher in older patients, patients who are receiving higher doses, who have an underlying hearing loss, who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside or who have underlying renal impairment. Monitor for signs and symptoms of ototoxicity during therapy. Monitor serum vancomycin concentrations and renal function in all patients receiving parenteral vancomycin. Discontinue Vancomycin Injection, USP if ototoxicity occurs. Dosage of Vancomycin Injection, USP must be adjusted for patients with renal impairment. Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.

Clostridium Difficile-Associated Diarrhea (CDAD)

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including vancomycin 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 antibacterial 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 antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

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 Injection, USP 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.

Hemorrhagic Occlusive Retinal Vasculitis (HORV)

Hemorrhagic occlusive retinal vasculitis, including permanent loss of vision, occurred in patients receiving intracameral or intravitreal administration of vancomycin during or after cataract surgery. The safety and efficacy of vancomycin administered by the intracameral or the intravitreal route have not been established by adequate and well-controlled trials. Vancomycin is not indicated for the prophylaxis of endophthalmitis.

Neutropenia

Reversible neutropenia has been reported in patients receiving vancomycin. 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.

Phlebitis and Other Administration Site Reactions

Inflammation at the site of injection of vancomycin has been reported. Vancomycin is irritating to tissue and must be given by a secure intravenous route of administration to reduce the risk of local irritation and phlebitis.

Administration of vancomycin by intramuscular (IM), intraperitoneal, intrathecal (intralumbar or intraventricular), or intravitreal routes has not been approved and is not recommended. 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.

Pain, tenderness, and necrosis occur with IM injection of vancomycin or with inadvertent extravasation. Thrombophlebitis may occur, the frequency and severity of which can be minimized by slow infusion of the drug and by rotation of venous access sites.

Intraperitoneal administration during continuous ambulatory peritoneal dialysis (CAPD) can result in chemical peritonitis. Manifestations range from cloudy dialysate alone to a cloudy dialysate accompanied by variable degrees of abdominal pain and fever. This syndrome appears to be resolved after discontinuation of intraperitoneal vancomycin.

Development of Drug-Resistant Bacteria

Prescribing Vancomycin 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.

Safe Implementation Strategies

Given the FDA BOXED WARNING contraindication of VANCO READY™ in pregnant women, **hospitals/EDs and other institutions that may encounter women of childbearing age at risk for sepsis will need to employ a Safe Implementation Strategy for VANCO READY™.**

Per the manufacturer, the following implementation strategy options are available for consideration by institutions. Sample protocol-update toolkits are available for use in multiple existing electronic health records (EHR) systems including EPIC, Meditech, and Cerner electronic medical record [EMR] systems.

- **Option 1:** Dispense VANCO READY™ to men and non–childbearing-age women only
- **Option 2:** Dispense to men and all women (with negative pregnancy tests for childbearing-age women, and/or women w/relevant patient history not at risk for pregnancy, eg, tubal ligation, hysterectomy, etc)
- **Customized Local Options,** which may incorporate patient history/patient narrative elements
- **For all options, employ smart-dispensing logic and hard-stop alerts wherever possible to prevent patient harm from "alarm fatigue"**
- **Block dispensing on all patients with a confirmed or unknown pregnancy status** without prior authorization

General Safe Dispensing Implementation Recommendations for VANCO READY™

1. Evaluate existing EHR and medication dispensing systems
2. Update electronic medical record systems with appropriate safe dispensing protocols
3. Utilize safe dispensing protocols in ADCs and central pharmacy automation
4. Incorporate unique product barcodes in the IV workflow system and ADC system to guide dispensing and restocking
5. Incorporate unique product barcodes in the EMR to support bedside barcode medication administration (BCMA)
6. Develop educational plan for pharmacy and nursing staff

P&T Committee Considerations

Given the high disease burden and associated costs of sepsis, along with rising incidences of infections at high risk for sepsis, local Pharmacy & Therapeutics (P&T) committees must incorporate the rapidly evolving regulatory and clinical-practice guideline landscape into their local decision-making. Novel medication-management standards and practice guidelines published between 2014 and 2018 by ISMP, ASHP, and The Joint Commission have all prioritized the use of commercially prepared, RTU infusible products in standardized dosages whenever they exist to reduce the potential of medication errors and improve patient safety.[79-81] Furthermore, FDA regulations require that any facility doing large-scale compounding receive federal 503b designation. Facilities that operate outside of 503b regulations may face federal penalties, including FDA warning letters, fines, drug recalls, and other penalties. All of these factors make a compelling clinical case for incorporation of premix antibiotics such as VANCO READY™ into local formulary stock.

Of particular interest to the P&T cohort, there are compelling cost- and efficiency-related reasons for making these agents standard use in EDs for sepsis treatment. Because the use of premix antimicrobials removed the necessity of admixing or other patient-level manipulation of medications by pharmacy and/or nursing staff, incorporation of RTU premix antimicrobial agents offers institutions an opportunity to achieve the following[65,66,98-100]:

- **Reduce the potential for admixing errors**
- **Improve efficiency and patient safety in the ED and CCU**
- **Improve adherence to ASHP/Joint Commission medication management standards**
- **Improve time-to-delivery of medications to patients with fewer labor handoffs or supply-chain delays**
- **Minimize drug waste/costs**

Of note, it can take significantly longer to deliver admixed antimicrobials from the pharmacy than it takes to deliver premix agents from an ADC right in the ED or CCU, which can impede institutions' ability to adhere to guideline-recommended time-to-treat in sepsis care.

While there is a paucity of US data surrounding the cost-benefit analysis of automated dispensing of premix IV antimicrobial agents, there is a limited amount of overseas data that support the long-term cost-benefit of premix IV agents in critical care/postoperative patients. For example, a 2002 Belgian study determined that use of premix RTU dobutamine in a postoperative cardiopulmonary bypass patient population resulted in a 60% reduction in drug cost versus traditional admix dobutamine, and a 32% reduction in IV nursing labor/preparation time in the premix group versus the traditional admix group.[101] Reports from nursing and pharmacy staff at a single US hospital that incorporated use of a frozen premix antibiotic to its in-house practices in 2011 also found it yielded overall cost reductions.[102]

To date, there are no specific US-based studies on the cost-benefit of premix IV medications versus compounded/reconstituted options. Meanwhile, a 2014 study from a Colombian hospital compared overall cost-per-dose of IV dopamine via multiple formulations: premix, compounding center, and in-ICU compounding. That cost comparison found that premix IV dopamine per dose costs were lowest at USD$47,625, versus USD$101,934 for compounding-center MINIBAG Plus and USD$108,870 for the local ICU-compounded drug. These compelling data indicate that premix IV agents can save significant costs while offering lower risk of dispensing errors and compounding-related contamination.[103] **Further elucidating these data, a 2014 Brazilian study found that use of ADCs reduces overall medication dispensing and related labor costs in CCUs.[104] No other studies of this nature were available in the worldwide literature at press time; however, institutions are advised to stay abreast of new developments.**

TABLE 4. Reasons Cited for Storing Premixed Formulations in Automated Dispensing Cabinets[99]

Factor	Number of Respondents (%)	
	Primary	*Secondary*
Efficiency	408 (68.3)	173 (30.6)
Frequent use	60 (10.2)	344 (60.9)
Pharmacy hours	43 (7.2)	29 (5.1)
Safety	30 (5.1)	219 (38.8)

Adapted from Fanikos J, Erickson A, Munz KE, Sanborn MD, Ludwig BC, Van Hassel T. Observations on the use of ready-to-use and point-of-care activated products in automated dispensing cabinets in U.S. hospitals. *Am J Health Syst Pharm*. 2007;64(19):2037-2043.

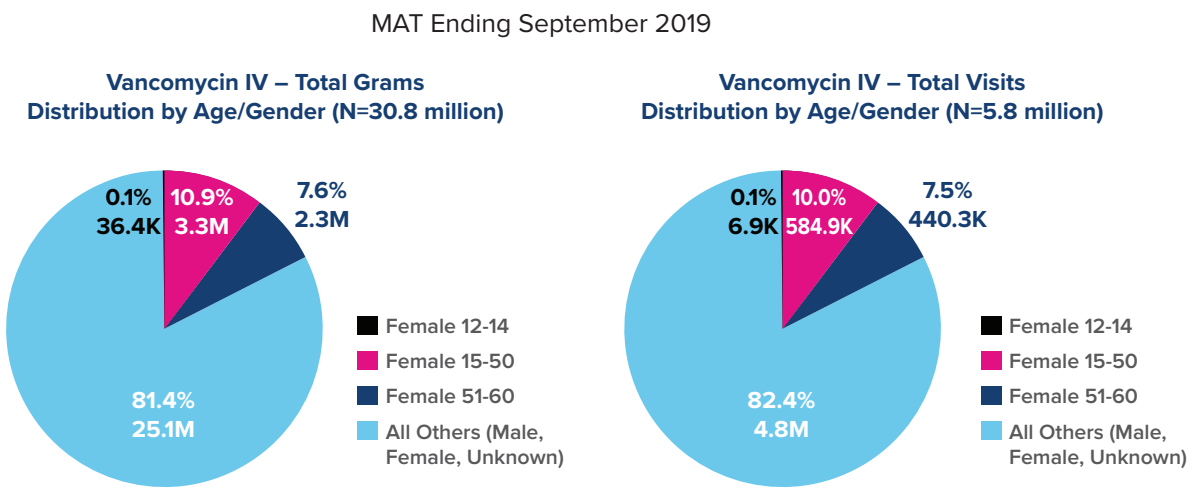
The ASHP has also collected survey data from US hospitals supporting the safety, efficiency, and cost-containment advantages of using ADCs whenever possible **(Table 4)**.[99] VANCO READY™ offers P&T committees the cost savings and efficiency advantage of ADC dispensing, currently the only vancomycin IV product that offers the necessary shelf-stability for in-unit ADCs.

P&T Strategies for Safe Dispensing of VANCO READY™ per Black Box Warning

Anecdotal reports indicate local P&T committees have expressed concerns regarding the safe use and implementation of VANCO READY™ given its contraindication in pregnancy, when non-premix/non–shelf-stable formulations that are not compatible with ADC dispensing do not include a similar warning.[105] These concerns can be addressed through use of safe implementation strategies described on **page 24**. Once safely implemented, use of VANCO READY™ can be used in a majority of patients. However, data indicate that 81% to 89% of all vancomycin grams are dispensed to males or females outside of childbearing age (eg, males and females under age 12 and over age 60, and/or males and females under age 12 and over age 50, and/or males and females without a documented pregnancy-related DRG), while only 0.6% of all vancomycin grams dispensed are given to patients with a documented pregnancy-related DRG **(Figures 3,4,5)**.[106]

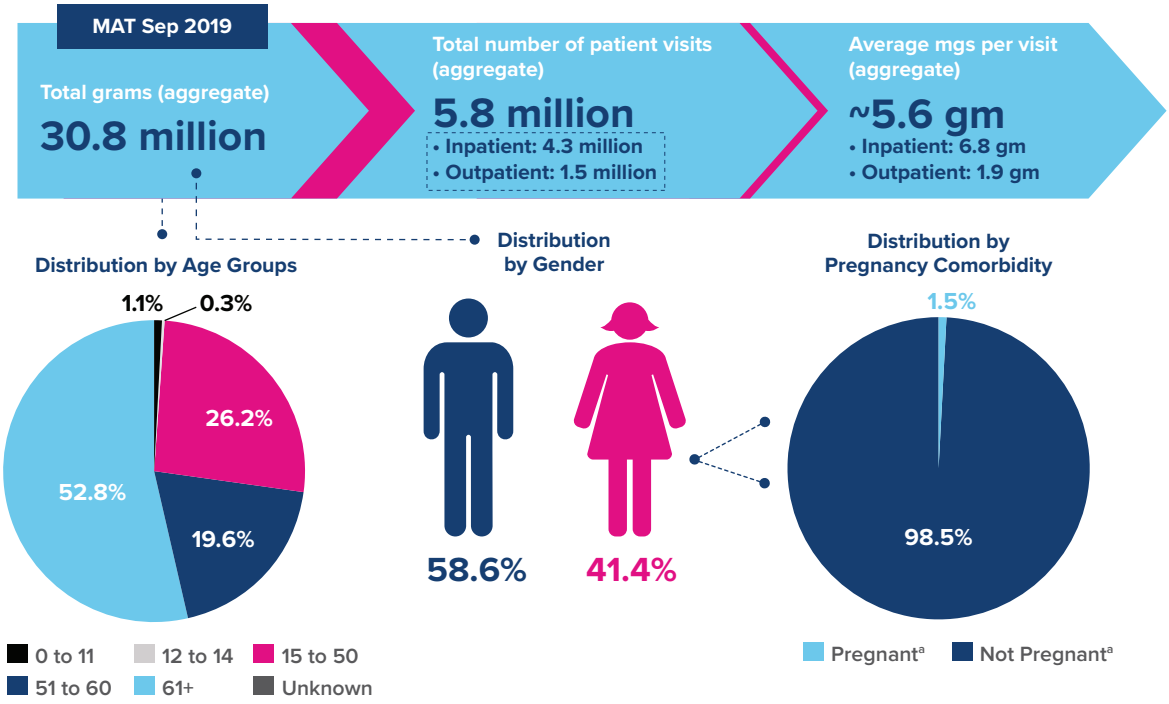
Of note, **VANCO READY™ is not subject to a REMS program**, simplifying its implementation and related reporting.

FIGURE 3. Only 10%-20% of Vancomycin IV mgs/Hospital Visits Are Administered to Female Patients of Child-bearing Age.[106]



Source: Charge Data Master (CDM) | Projected Results.

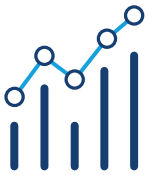
FIGURE 4. In MAT September 2019, 30.8 Million Grams of IV Vancomycin Were Administered in the Hospital Setting Across 5.8 Million Visits.[106]



[a]This study found documented pregnancy-related DRGs, which is not an exact surrogate for pregnancy.

Source: Charge Data Master (CDM) | Projected Results | Unknown Gender not shown (0.01%).

FIGURE 5. IQVIA's CDM Dataset, Which Is Collected From ~400 Short-Term, General Non-Federal Hospitals, Was Leveraged for This Analysis.[106]

Summary		
What	• IQVIA's Charge Data Master (CDM) asset provides unique insights into what happens and how patients are being treated during hospital visits	
Where	• CDM data are collected from approximately 350-400 Short-Term, General Non-Federal Hospitals (STGNF)	
How	• The Charge Data Master is an accounting system specific to each hospital • Unlike standard hospital claim data (collected through a UB-04 form), CDM tracks patients from all pay types and provides a greater level of detail about what happens during hospital visits	

Per patient population data, local P&T institutions should evaluate available evidence-based Safe Implementation Dispensing Protocols and make local implementation decisions accordingly, working in partnership with their institutional Antimicrobial Stewardship Teams to ensure IV vancomycin use practices are in alignment with their local antimicrobial resistance antibiograms **(Figure 6)**.

FIGURE 6. General Safe Dispensing Implementation Recommendations for VANCO READY™

Incorporating steps into locally preferred protocols and procedures, P&T Committees can establish safe dispensing protocols for VANCO READY™ that meet the needs of local patient population(s).

1. Evaluate existing EHR and medication dispensing systems
2. Update EMR systems with appropriate safe-dispensing protocols
3. Utilize safe-dispensing protocols in ADCs and central pharmacy automation
4. Incorporate unique product barcodes in the IV workflow and ADC systems to guide dispensing and restocking
5. Incorporate unique product barcodes in the EMR to support BCMA
6. Develop educational plan for pharmacy and nursing staff
7. Partner with local antimicrobial stewardship committee for appropriate dispensing/empirical use protocols

Conclusions

Because sepsis (septicemia) is associated with ever-increasing frequency and mortality,[3-7] improving the quality of sepsis care should be a top priority for US healthcare institutions. The prompt selection and dispensing of effective antibiotics for all at-risk infections generally and by improving time-to-treat with effective antibiotics (eg, within 1 hour) when patients present with identifiable sepsis symptoms specifically has been shown to improve sepsis survival and is also in line with clinical practice guidelines and measure sets issued by the CMS Surviving Sepsis Campaign.[6-10]

VANCO READY™ offers local P&T committees a novel option that better adheres to emerging regulatory and guideline/accreditation requirements prioritizing premix antibiotics for managing sepsis and related high-risk infections. This product provides the same antimicrobial efficacy as legacy formulations with simpler dispensing/storage requirements and longer shelf-life. **While this product's excipient stabilizers polyethylene glycol (PEG) 400 and N-acetyl-D-alanine (NADA) constitute a contraindication in pregnancy, only 0.6% of all vancomycin grams dispensed are given to patients with a pregnancy-related DRG.[106] This small patient cohort plus evidence-based implementation of safe dispensing protocols in local institutions can allow for low-risk use of premix vancomycin in appropriate subpopulations.**

Given available clinical and cost-benefit evidence, P&T committees at local institutions have multiple compelling reasons to incorporate shelf-stable, premix antibiotics managed by ADCs, including dispensing protocols into their EDs and CCUs, which are supported by multiple regulators and accrediting bodies. Prompt adoption of IV premix vancomycin also has the potential to help local P&T departments contribute to overall cost-reduction, labor efficiencies, and improved patient safety in their institutions while reducing drug waste/spoilage.[65,66,99,100,103,106]

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Important Safety Information

VANCOMYCIN INJECTION
INDICATIONS AND USAGE

Vancomycin Injection is a glycopeptide antibacterial indicated in adult and pediatric patients (1 month and older) for the treatment of:

- Septicemia (1.1)
- Infective Endocarditis (1.2)
- Skin and Skin Structure Infections (1.3)
- Bone Infections (1.4)
- Lower Respiratory Tract Infections (1.5)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Vancomycin Injection and other antibacterial drugs, Vancomycin Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. (1.6)

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF EMBRYO-FETAL TOXICITY DUE TO EXCIPIENTS

This formulation of Vancomycin Injection is not recommended for use during pregnancy because it contains the excipients polyethylene glycol (PEG 400) and N-acetyl D-alanine (NADA), which caused fetal malformations in animal reproduction studies. If use of vancomycin is needed during pregnancy, use other available formulations of vancomycin. (5.1, 8.1)

DOSAGE AND ADMINISTRATION

Use this formulation of Vancomycin Injection only in patients who require the entire (500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g, or 2 g) dose and not any fraction thereof. (2.1)

For intravenous use only. Do Not administer orally.

Administer Vancomycin Injection by intravenous infusion over 60 minutes or greater to reduce the risk of infusion reactions (2.1)

Adult Patients: 2 g divided either as 0.5 grams (g) every 6 hours or 1 g every 12 hours (2.2)

Pediatric Patients (1 Month and Older): 10 mg/kg per dose given every 6 hours (2.3)

Patients with Renal Impairment: See full prescribing information for recommended doses in patients with renal impairment (2.4)

See full prescribing information for further important administration and preparation instructions (2.1, 2.5)

DOSAGE FORMS AND STRENGTHS

Vancomycin Injection: Single-dose flexible bags containing 500 mg vancomycin in 100 mL, 750 mg vancomycin in 150 mL, 1 g vancomycin in 200 mL, 1.25 g vancomycin in 250 mL, 1.5 g vancomycin in 300 mL, 1.75 g vancomycin in 350 mL and 2 g vancomycin in 400 mL of liquid (3).

CONTRAINDICATIONS

Hypersensitivity to vancomycin (4)

WARNINGS AND PRECAUTIONS

Infusion Reactions: Hypotension, including shock and cardiac arrest, wheezing, dyspnea, urticaria, muscular and chest pain and "red man syndrome" which manifests as pruritus and erythema that involves the face, neck and upper torso may occur with rapid intravenous administration. To reduce the risk of infusion reactions, administer Vancomycin Injection over a period of 60 minutes or greater and also prior to intravenous anesthetic agents. (2.1, 5.2)

Nephrotoxicity: Systemic vancomycin exposure may result in acute kidney injury (AKI) including acute renal failure, mainly due to interstitial nephritis or less commonly acute tubular necrosis. Monitor serum vancomycin concentrations and renal function. (5.3)

Ototoxicity: Ototoxicity has occurred in patients receiving vancomycin. Monitor for signs and symptoms of ototoxicity during therapy. Monitor serum vancomycin concentrations and renal function. Assessment of auditory function may be appropriate in some instances. (5.4)

Clostridium Difficile-Associated Diarrhea: Evaluate patients if diarrhea occurs. (5.5).

Neutropenia: Periodically monitor leukocyte count. (5.7)

Phlebitis: To reduce the risk of local irritation and phlebitis administer Vancomycin Injection by a secure intravenous route of administration. (5.8)

Development of Drug-Resistant Bacteria: Prescribing Vancomycin Injection in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria. (5.9)

ADVERSE REACTIONS

The common adverse reactions are anaphylaxis, "red man syndrome", acute kidney injury, hearing loss, neutropenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Xellia Pharmaceuticals USA, LLC at 1-833-295-6953 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Anesthetic Agents: Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing. (2.1, 7.1)

Piperacillin/Tazobactam: Increased incidence of acute kidney injury in patients receiving concomitant piperacillin/tazobactam and vancomycin as compared to vancomycin alone. Monitor kidney function in patients (7.2)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VANCOMYCIN INJECTION, USP safely and effectively. See full prescribing information for VANCOMYCIN INJECTION, USP.

VANCOMYCIN injection, f or intravenous use Initial U.S. Approval: 1958

WARNING: RISK OF EMBRYO-FETAL TOXICITY DUE TO EXCIPIENTS

See full prescribing information for complete boxed warning.

This formulation of Vancomycin Injection, USP is not recommended for use during pregnancy because it contains the excipients polyethylene glycol (PEG 400) and N-acetyl D-alanine (NADA), which caused fetal malformations in animal reproduction studies. If use of vancomycin is needed during pregnancy, use other available formulations of vancomycin. (5.1, 8.1)

INDICATIONS AND USAGE

Vancomycin Injection, USP is a glycopeptide antibacterial indicated in adult and pediatric patients (1 month and older) for the treatment of:

- Septicemia (1.1)
- Infective Endocarditis (1.2)
- Skin and Skin Structure Infections (1.3)
- Bone Infections (1.4)
- Lower Respiratory Tract Infections (1.5)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Vancomycin Injection, USP and other antibacterial drugs, Vancomycin Injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. (1.6)

DOSAGE AND ADMINISTRATION

- Use this formulation of Vancomycin Injection, USP only in patients who require the entire (500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g or 2 g) dose and not any fraction thereof. (2.1)
- For intravenous use only. Do **Not** administer orally.
- Administer Vancomycin Injection, USP by intravenous infusion over 60 minutes or greater to reduce the risk of infusion reactions (2.1)
- Adult Patients: 2 g divided either as 0.5 grams (g) every 6 hours or 1 g every 12 hours (2.2)
- Pediatric Patients (1 Month and Older): 10 mg/kg per dose given every 6 hours (2.3)
- Patients with Renal Impairment: See full prescribing information for recommended doses in patients with renal impairment (2.4)
- See full prescribing information for further important administration and preparation instructions (2.1, 2.5)

DOSAGE FORMS AND STRENGTHS

Vancomycin Injection, USP: Single-dose flexible bags containing 500 mg vancomycin in 100 mL, 750 mg vancomycin in 150 mL, 1 g vancomycin in 200 mL, 1.25 g vancomycin in 250 mL, 1.5 g vancomycin in 300 mL, 1.75 g vancomycin in 350 mL and 2 g vancomycin in 400 mL of liquid. (3)

CONTRAINDICATIONS

Hypersensitivity to vancomycin (4)

WARNINGS AND PRECAUTIONS

- Infusion Reactions: Hypotension, including shock and cardiac arrest, wheezing, dyspnea, urticaria, muscular and chest pain and "red man syndrome" which manifests as pruritus and erythema that involves the face, neck and upper torso may occur with rapid intravenous administration. To reduce the risk of infusion reactions, administer Vancomycin Injection, USP over a period of 60 minutes or greater and also prior to intravenous anesthetic agents. (2.1, 5.2)
- Nephrotoxicity: Systemic vancomycin exposure may result in acute kidney injury (AKI) including acute renal failure, mainly due to interstitial nephritis or less commonly acute tubular necrosis. Monitor serum vancomycin concentrations and renal function. (5.3)
- Ototoxicity: Ototoxicity has occurred in patients receiving vancomycin. Monitor for signs and symptoms of ototoxicity during therapy. Monitor serum vancomycin concentrations and renal function. Assessment of auditory function may be appropriate in some instances. (5.4)
- *Clostridium Difficile*-Associated Diarrhea: Evaluate patients if diarrhea occurs. (5.5).
- Neutropenia: Periodically monitor leukocyte count. (5.7)
- Phlebitis: To reduce the risk of local irritation and phlebitis administer Vancomycin Injection, USP by a secure intravenous route of administration. (5.8)
- Development of Drug-Resistant Bacteria: Prescribing Vancomycin Injection, USP in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria. (5.9)

ADVERSE REACTIONS

The common adverse reactions are anaphylaxis, "red man syndrome", acute kidney injury, hearing loss, neutropenia. (6.1) **To report SUSPECTED ADVERSE REACTIONS, contact Xellia Pharmaceuticals USA, LLC at 1-833-295-6953 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

DRUGS INTERACTIONS

- Anesthetic Agents: Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing. (2.1, 7.1)
- Piperacillin/Tazobactam: Increased incidence of acute kidney injury in patients receiving concomitant piperacillin/tazobactam and vancomycin as compared to vancomycin alone. Monitor kidney function in patients. (7.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF EMBRYO-FETAL TOXICITY DUE TO EXCIPIENTS

This formulation of Vancomycin Injection, USP is not recommended for use during pregnancy because it contains the excipients polyethylene glycol (PEG) 400 and N-acetyl- D-alanine (NADA), which caused fetal malformations in animal reproduction studies. If use of vancomycin is needed during pregnancy, use other available formulations of vancomycin *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

1 INDICATIONS AND USAGE

1.1 Septicemia

Vancomycin Injection, USP is indicated in adults and pediatric patients (1 month and older) for the treatment of septicemia due to:

- Susceptible isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase negative staphylococci.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

1.2 Infective Endocarditis

Vancomycin Injection, USP is indicated in adults and pediatric patients (1 month and older) for the treatment of infective endocarditis due to:

- Susceptible isolates of MRSA.
- Viridans group streptococci *Streptococcus gallolyticus* (previously known as *Streptococcus bovis*), *Enterococcus* species and *Corynebacterium* species. For enterococcal endocarditis, use Vancomycin Injection, USP in combination with an aminoglycoside.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

Vancomycin Injection, USP is indicated in adults and pediatric patients (1 month and older) for the treatment of early-onset prosthetic valve endocarditis caused by *Staphylococcus epidermidis* in combination with rifampin and an aminoglycoside.

1.3 Skin and Skin Structure Infections

Vancomycin Injection, USP is indicated in adults and pediatric patients (1 month and older) for the treatment of skin and skin structure infections due to:

- Susceptible isolates of MRSA and coagulase negative staphylococci.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

1.4 Bone Infections

Vancomycin Injection, USP is indicated in adults and pediatric patients (1 month and older) for the treatment of bone infections due to:

- Susceptible isolates of MRSA and coagulase negative staphylococci.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

1.5 Lower Respiratory Tract Infections

Vancomycin Injection, USP is indicated in adults and pediatric patients (1 month and older) for the treatment of lower respiratory tract infections due to:

- Susceptible isolates of MRSA
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

1.6 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Vancomycin Injection, USP and other antibacterial drugs, Vancomycin 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Use this formulation of Vancomycin Injection, USP only in patients who require the entire (500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g or 2 g) dose and not any fraction thereof.

Vancomycin Injection, USP in transparent single-dose flexible bags are intended for intravenous use only. Do **NOT** administer orally.

To reduce the risk of infusion related adverse reactions, administer Vancomycin Injection, USP by intravenous infusion over 60 minutes or greater *[see Warnings and Precautions (5.2)* and *Adverse Reactions (6.1)]*. An infusion rate of 10 mg/min or less is associated with fewer infusion-related events *[see Warnings and Precautions (5.2)]*. Infusion related events may occur, however, at any rate or concentration.

Drug additives should not be made to this solution.

Vancomycin Injection, USP concentrations of no more than 5 mg/ mL are recommended in adults *[see Dosage and Administration (2.2)]*. See also age-specific recommendations *[see Dosage and Administration (2.3)]*.

Administer Vancomycin Injection, USP prior to intravenous anesthetic agents to reduce the risk of infusion related adverse reactions *[see Warnings and Precautions (5.2)]*.

Administer Vancomycin Injection, USP by a secure intravenous route of administration to avoid local irritation and phlebitis reactions *[see Warnings and Precautions (5.8)]*.

2.2 Dosage in Adult Patients with Normal Renal Function

The usual daily intravenous dose is 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours. Administer each dose by intravenous infusion over a period of 60 minutes or greater. Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose. The initial daily dose should be no less than 15 mg/kg.

2.3 Dosage in Pediatric Patients (1 Month and Older) with Normal Renal Function

Use this formulation of Vancomycin Injection, USP only in pediatric patients (1 month and older) who require the entire dose (500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g or 2 g) of this single-dose flexible bag and not any fraction of it *[see Dosage Forms and Strengths (3)]*.

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.

2.4 Dosage in Patients with Renal Impairment

Dosage adjustment must be made in patients with renal impairment. The initial dose should be no less than 15 mg/kg in patients with any degree of renal impairment.

In the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Measure trough vancomycin serum concentrations to guide therapy, especially in seriously ill patients with changing renal function.

For functionally anephric patients, an initial dose of 15 mg/kg of body weight should be given to achieve prompt therapeutic serum concentration. A dose of 1.9 mg/kg/24 h should be given after the initial dose of 15 mg/kg.

2.5 Directions for Use of Vancomycin Injection, USP and Storage Instructions

Vancomycin Injection, USP, in transparent single-dose flexible bag is for intravenous administration only.

Vancomycin Injection, USP is room temperature stable, ready-to- use drug product.

Preparation for Intravenous Administration:

1. Remove the flexible bag from aluminum overpouch.
2. Check for minute leaks by squeezing the bag firmly. If leaks are detected, discard solution because sterility may be impaired. Leaks may be more readily detected by wrapping the bag with blotting paper or a tissue before squeezing.
3. Do not add supplemental medication.
4. Visually inspect the flexible bag. If the outlet port protector is damaged, detached, or not present, discard the flexible bag as solution path sterility may be impaired. If after visual inspection the solution is cloudy or if an insoluble precipitate is noted or if any seals are not intact, the flexible bag should be discarded.
5. The solution in the flexible bag remains chemically stable for 28 days at room temperature (up to 25°C/77°F) after removal from the aluminum overpouch. Discard unused drug.
6. Suspend the flexible bag from eyelet support.
7. Remove protector from outlet port at bottom of flexible bag.
8. Attach administration set. Refer to complete directions accompanying set.
9. Use sterile equipment.

Do **NOT** use flexible bags in series connections. Such use could result in an embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

2.6 Incompatibilities for Intravenous Use

Vancomycin solution has a low pH and may cause chemical or physical instability when it is mixed with other compounds. Mixtures of solutions of vancomycin and beta-lactam antibacterial drugs 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 antibacterial drugs.

3 DOSAGE FORMS AND STRENGTHS

Vancomycin Injection, USP is a ready to use clear, colorless to light brown solution in single-dose flexible bags containing 500 mg vancomycin in 100 mL, 750 mg vancomycin in 150 mL, 1 g vancomycin in 200 mL, 1.25 g vancomycin in 250 mL, 1.5 g vancomycin in 300 mL, 1.75 g vancomycin in 350 mL and 2 g vancomycin in 400 mL of liquid *[see Description (11)]*. The flexible bags are supplied in sealed aluminum overpouches.

4 CONTRAINDICATIONS

Vancomycin Injection, USP is contraindicated in patients with known hypersensitivity to vancomycin.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Embryo-Fetal Toxicity Due to PEG 400 and NADA Excipients

This formulation of Vancomycin Injection, USP is not recommended during pregnancy because it contains the excipients PEG 400 and NADA, which caused fetal malformations in animal reproduction studies. The active ingredient vancomycin is not known to be associated with embryo-fetal toxicity *[see BOXED WARNING, Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1)]*.

Advise pregnant women of the potential risk to the fetus. If use of vancomycin is needed during pregnancy, use other available formulations of vancomycin.

5.2 Infusion Reactions

Hypotension, including shock and cardiac arrest, wheezing, dyspnea, urticaria, muscular and chest pain may occur with rapid Vancomycin Injection, USP administration. The reactions may be more severe in younger patients, particularly children, and in patients receiving concomitant muscle relaxant anesthetics.

Rapid intravenous administration of Vancomycin Injection, USP may also be associated with “red man syndrome”, which manifests as pruritus and erythema that involves the face, neck and upper torso.

Infusion-related adverse reactions are related to both the concentration and the rate of administration of vancomycin. Infusion-related adverse reactions may occur, however, at any rate or concentration.

Administer Vancomycin Injection, USP over a period of 60 minutes or greater to reduce the risk of infusion-related adverse reactions. 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 adverse reactions. Administer prior to intravenous anesthetic agents when feasible. Stop the infusion if a reaction occurs.

5.3 Nephrotoxicity

Vancomycin Injection, USP can result in acute kidney injury (AKI), including acute renal failure, mainly due to interstitial nephritis or less commonly acute tubular necrosis. AKI is manifested by increasing blood urea nitrogen (BUN) and serum creatinine (Cr). The risk of AKI increases with higher vancomycin serum levels, prolonged exposure, concomitant administration of other nephrotoxic drugs, concomitant administration of piperacillin- tazobactam *[see Drug Interactions (7.2)]*, volume depletion, pre-existing renal impairment and in critically ill patients and patients with co-morbid conditions that predispose to renal impairment.

Monitor serum vancomycin concentrations and renal function in all patients receiving Vancomycin Injection, USP. More frequent monitoring is recommended in patients with comorbidities that predispose to impairment in renal function or are concomitantly receiving other nephrotoxic drugs, in critically ill patients, in patients with changing renal function, and in patients requiring higher therapeutic vancomycin levels. If acute kidney injury occurs, discontinue Vancomycin Injection, USP or reduce the dose.

5.4 Ototoxicity

Ototoxicity has occurred in patients receiving vancomycin. It may be transient or permanent. Ototoxicity manifests as tinnitus, hearing loss, dizziness or vertigo. The risk is higher in older patients, patients who are receiving higher doses, who have an underlying hearing loss, who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside or who have underlying renal impairment. Monitor for signs and symptoms of ototoxicity during therapy. Monitor serum vancomycin concentrations and renal function in all patients receiving parenteral vancomycin. Discontinue Vancomycin Injection, USP if ototoxicity occurs. Dosage of Vancomycin Injection, USP must be adjusted for patients with renal impairment *[see Dosage and Administration (2.3)]*. Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.

5.5 *Clostridium Difficile*-Associated Diarrhea (CDAD)

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including vancomycin 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 antibacterial 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 antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

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 Injection, USP 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.

5.6 Hemorrhagic Occlusive Retinal Vasculitis (HORV)

Hemorrhagic occlusive retinal vasculitis, including permanent loss of vision, occurred in patients receiving intracameral or intravitreal administration of vancomycin during or after cataract surgery. The safety and efficacy of vancomycin administered by the intracameral or the intravitreal route have not been established by adequate and well-controlled trials. Vancomycin is not indicated for the prophylaxis of endophthalmitis.

5.7 Neutropenia

Reversible neutropenia has been reported in patients receiving vancomycin *[see Adverse Reactions (6.1)]*. 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.

5.8 Phlebitis and Other Administration Site Reactions

Inflammation at the site of injection of vancomycin has been reported. Vancomycin is irritating to tissue and must be given by a secure intravenous route of administration to reduce the risk of local irritation and phlebitis.

Administration of vancomycin by intramuscular (IM), intraperitoneal, intrathecal (intralumbar or intraventricular), or intravitreal routes has not been approved and is not recommended. 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.

Pain, tenderness, and necrosis occur with IM injection of vancomycin or with inadvertent extravasation. Thrombophlebitis may occur, the frequency and severity of which can be minimized by slow infusion of the drug and by rotation of venous access sites.

Intraperitoneal administration during continuous ambulatory peritoneal dialysis (CAPD) can result in chemical peritonitis. Manifestations range from cloudy dialysate alone to a cloudy dialysate accompanied by variable degrees of abdominal pain and fever. This syndrome appears to be resolved after discontinuation of intraperitoneal vancomycin.

5.9 Development of Drug-Resistant Bacteria

Prescribing Vancomycin 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.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions *[see Warnings and Precautions (5.2)]*
- Nephrotoxicity *[see Warnings and Precautions (5.3)]*
- Ototoxicity *[see Warnings and Precautions (5.4)]*
- *Clostridium Difficile*-Associated Diarrhea *[see Warnings and Precautions (5.5)]*
- Hemorrhagic Occlusive Retinal Vasculitis *[see Warnings and Precautions (5.6)]*
- Neutropenia *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following adverse reactions associated with the use of vancomycin were identified in clinical trials:

Immune system disorders: Hypersensitivity reactions including anaphylaxis and "red man syndrome" *[see Warnings and Precautions (5.2)]*

Skin and subcutaneous tissue disorders: Erythema (especially of the face, neck and upper torso) and pruritus which are manifestations of rashes including exfoliative dermatitis, linear IgA bullous dermatosis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Renal and urinary disorders: Acute kidney injury and interstitial nephritis

Ear and Labyrinth Disorders: Tinnitus, hearing loss, vertigo

Blood and Lymphatic System Disorders: Agranulocytosis, neutropenia, pancytopenia, leukopenia, thrombocytopenia, eosinophilia

Gastrointestinal Disorders: Pseudomembranous colitis *[see Warnings and Precautions (5.5)]*

Cardiac Disorders: Cardiac arrest, chest pain

General Disorders and Administration Site Conditions: General discomfort, fever, chills, phlebitis, injection site irritation, injection site pain and necrosis following intramuscular injection, chemical peritonitis following intraperitoneal administration (Vancomycin Injection, USP is not approved for intramuscular and intraperitoneal administration) *[see Warnings and Precautions (5.8)]*

Laboratory Abnormalities: Elevated blood urea nitrogen, elevated serum creatinine

Musculoskeletal and connective tissue disorders: Muscle pain

Nervous system disorders: Dizziness

Respiratory, thoracic and mediastinal disorders: Wheezing, dyspnea

Vascular disorders: Hypotension, shock, vasculitis

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing 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)

7 DRUG INTERACTIONS

7.1 Anesthetic Agents

Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.4)]*.

7.2 Piperacillin-Tazobactam

Studies have detected an increased incidence of acute kidney injury in patients administered concomitant piperacillin/tazobactam and vancomycin as compared to vancomycin alone. Monitor kidney function in patients receiving concomitant piperacillin/tazobactam and vancomycin. No pharmacokinetic interactions have been noted between piperacillin/tazobactam and vancomycin.

7.3 Ototoxic and/or Nephrotoxic Drugs

Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs requires more frequent monitoring of renal function.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

This formulation of Vancomycin Injection, USP is not recommended for use during pregnancy because it contains the excipients, PEG 400 and NADA, which caused fetal malformations in animal reproduction studies *(see Data)*. Advise pregnant women of the potential risk to the fetus. If therapy with vancomycin is needed during pregnancy, use other available formulations of vancomycin.

There are no available data on vancomycin use in pregnant women to inform a drug-associated risk of major birth defects or miscarriage. Available published data on vancomycin use in pregnancy during the second and third trimesters have not shown an association with adverse pregnancy related outcomes *(see Data)*. There are no available data on first trimester use of vancomycin, including vancomycin with the excipients PEG 400 and NADA, in pregnant women to assess the risk of major birth defects or miscarriage. Vancomycin alone did not show adverse developmental effects when administered intravenously to pregnant rats and rabbits during organogenesis at doses less than or equal to the recommended maximum human dose based on body surface area.

Reproduction studies in rabbits with intravenous doses of PEG 400 at approximately 5 times the maximum daily human dose based on body surface area comparisons administered during organogenesis resulted in fetal spinal malformations. Reproduction studies in rabbits and rats using intravenous doses of NADA at approximately 6 and 7 times the maximum daily human dose, respectively, based on body surface comparisons resulted in maternal toxicity and fetal spinal and cardiovascular malformations in rabbits, and maternal toxicity with no significant adverse embryo-fetal effects in rats. Vancomycin alone did not show adverse developmental effects when administered intravenously to pregnant rats and rabbits during organogenesis at doses less than or equal to the recommended maximum human dose based on body surface area *(see Data)*.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

There are no available data on first trimester use of vancomycin, including vancomycin with the excipients PEG 400 and NADA, in pregnant women to assess a risk of major birth defects or miscarriage.

A published study evaluated hearing loss and nephrotoxicity in infants of 10 pregnant intravenous drug users treated with vancomycin (formulation did not include the excipients PEG 400 and NADA) for suspected or documented methicillin-resistant *Staphylococcus aureus* in the second or third trimester. The comparison groups were 10 uninfected non-intravenous drug-dependent patients, and 10 uninfected intravenous drug- dependent patients who served as substance abuse controls. No infant in the vancomycin exposed group had abnormal sensorineural hearing at 3 months of age or nephrotoxicity.

A published prospective study assessed outcomes in 55 pregnant women with a positive Group B streptococcus (GBS) culture and a high-risk penicillin allergy with resistance to clindamycin or unknown sensitivity who were administered vancomycin (formulation did not include the excipients PEG 400 and NADA) at the time of delivery. Vancomycin dosing ranged from the standard 1 g intravenously every 12 hours to 20 mg/kg intravenous every 8 hours (maximum individual dose 2 g). No major adverse reactions were recorded either in the mothers or their newborns. None of the newborns had sensorineural hearing loss. Neonatal renal function was not examined, but all of the newborns were discharged in good condition.

Animal Data

Vancomycin did not cause fetal malformations when administered during organogenesis to pregnant rats (gestation days 6 to 15) and rabbits (gestation days 6 to 18) at the equivalent recommended maximum human dose (based on body surface area comparisons) of 200 mg/kg/day IV to rats or 120 mg/kg/day IV to rabbits. No effects on fetal weight or development were seen in rats at the highest dose tested or in rabbits given 80 mg/kg/ day (approximately 1 and 0.8 times the recommended maximum human dose based on body surface area, respectively). Maternal toxicity was observed in rats (at doses 120 mg/kg and above) and rabbits (at 80 mg/kg and above).

Animal reproduction studies conducted in rabbits administered intravenous PEG 400 at 2000 mg/kg (approximately 5 times the maximum daily human dose, based on body surface comparisons) during organogenesis (gestation days 6 to 19) resulted in fetal scoliosis (thoracic and lumbar) and increased incidence of delayed or incomplete ossification of the pubes, epiphyses, and talus bones. No maternal toxicity was observed up to the maximum dose tested.

Similarly, in animal reproduction studies conducted in pregnant rabbits (gestation days 6 to 19) and pregnant rats (gestation days 6 to 17) administered intravenous NADA at 1680 and 3780 mg/kg, respectively (approximately 6 and 7 times the maximum daily human dose, respectively, based on body surface area comparisons) resulted in fetal scoliosis and a spectrum of rare cardiovascular anomalies in rabbits and no adverse effects on fetuses in rats. Increased incidence of delayed or incomplete ossifications of the metacarpals/metatarsals/ phalanges and increased ossification (fused jugal/maxilla bones) were observed in rabbits at 1680 mg/kg. Minor fetal skeletal abnormalities were observed in rats at 3780 mg/kg which was also associated with maternal toxicity including increased incidence of litter loss.

No animal studies have been conducted to evaluate the potential reproductive and embryo-fetal effects of Vancomycin Injection, USP.

8.2 Lactation

Risk Summary

There are insufficient data to inform the levels of vancomycin in human milk. There are no data on the effects of vancomycin on the breastfed infant or milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for vancomycin and any potential adverse effects on the breastfed infant from vancomycin or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Perform a pregnancy test in females of reproductive potential prior to prescribing this formulation of vancomycin *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

8.4 Pediatric Use

Vancomycin Injection, USP is indicated in pediatric patients (1 month and older) *[see Indications and Usage (1.1 to 1.5) and Dosage and Administration (2.2)]*. In pediatric patients, monitor vancomycin serum concentration and renal function when administering Vancomycin Injection, USP *[see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.3)]*. More severe infusion related reactions related to vancomycin administration may occur in pediatric patients. Concomitant administration of vancomycin and intravenous anesthetic agents has been associated with erythema and histamine-like flushing in all patients including pediatric patients *[see Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

Vancomycin is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection *[see Dosage and Administration (2.2)]*, and it may be useful to monitor renal function *[see Warnings and Precautions (5.3)]*.

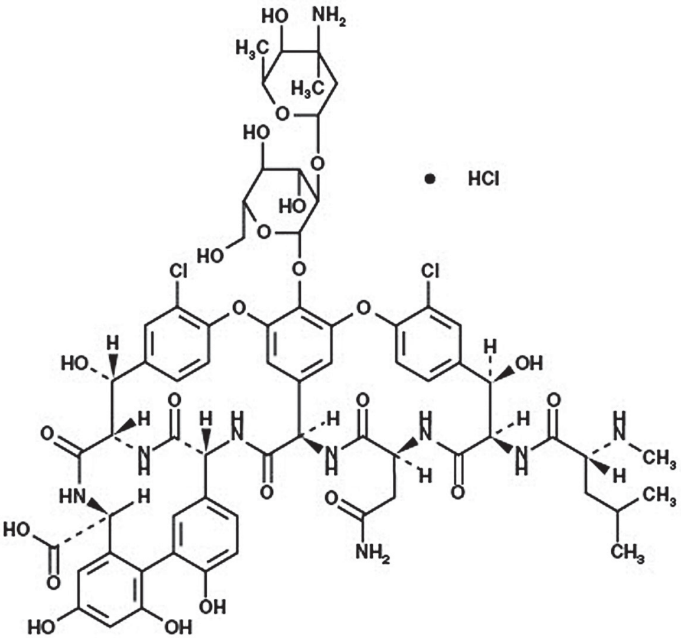
10 OVERDOSAGE

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.

For current information on the management of overdosage, contact the National Poison Control Center at 1-800-222-1222 or www.poison.org.

11 DESCRIPTION

Vancomycin Injection, USP, in single-dose flexible bags contain vancomycin as vancomycin hydrochloride. It is a tricyclic glycopeptide antibacterial drug derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*). The molecular formula is $C_{66}H_{75}Cl_2N_9O_{24}$•HCl and the molecular weight is 1,485.71. The chemical name is (Sa)-(3S,6R,7R,22R,23S,26S,36R,38aR)-44-{[2-O-(3-amino-2,3,6-trideoxy-3-C-methylα-L-lyxo-hexopyranosyl)-β-D-glucopyranosyl]-oxy}-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38atetradeca hydro-7,22,28,30,32-pentahydroxy-6-[(2R)-4-methyl-2-(methylamino]valeramido]-2,5,24,38,39-pentaoxo-22H-8,11:18,21-dietheno23,36(iminomethano)-13,16:31,35-dimetheno1H,16H-[1,6,9]-oxadiazacyclohexadecino-[4,5-m][10,2,16]-benzoxadiazacyclotetracosine-26-carboxylic acid, monohydrochloride. Vancomycin hydrochloride has the following structural formula:



Vancomycin Injection, USP, in single-dose flexible bags are sterile, nonpyrogenic premixed 100 mL, 150 mL, 200 mL, 250 mL, 300 mL, 350 mL or 400 mL solution containing 500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g or 2 g vancomycin, respectively, as vancomycin hydrochloride. Each 100 mL of solution contains 1.8 mL polyethylene glycol 400, 1.36 g N-acetyl-D-alanine, 1.26 g L-lysine hydrochloride (monochloride) in water for injection. Hydrochloric acid and sodium hydroxide are used for pH adjustment. The pH is 4.5 to 5.5 and the osmolarity is 350 to 475 mOsmol/L.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vancomycin is an antibacterial drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

The pharmacodynamics of vancomycin is unknown.

12.3 Pharmacokinetics

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 like those after a single dose.

Distribution

The volume of distribution ranges from 0.3 to 0.43 L/kg after intravenous administration.

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.

Elimination

Mean plasma clearance is about 0.058 L/kg/h, and mean renal clearance is about 0.048 L/kg/h. The mean elimination half-life of vancomycin from plasma is 4 to 6 hours in subjects with normal renal function. In anephric patients, the mean elimination half-life is 7.5 days. Total body and renal clearance of vancomycin may be reduced in the elderly.

Metabolism

There is no apparent metabolism of the vancomycin.

Excretion

In the first 24 hours after intravenous administration, about 75% of an administered dose of vancomycin is excreted in urine by glomerular filtration. Renal impairment slows excretion of vancomycin.

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 Warnings and Precautions (5.7)]*.

12.4 Microbiology

Mechanism of Action

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

Resistance

Vancomycin is not active *in vitro* against gram-negative bacilli, mycobacteria, or fungi. There is no cross-resistance between vancomycin and other antibacterials.

Interaction with Other Antimicrobials

The combination of vancomycin and an aminoglycoside acts synergistically *in vitro* against many isolates of *Staphylococcus aureus*, *Streptococcus gallolyticus* (previously known as *Streptococcus bovis*), *Enterococcus* spp, and the viridans group streptococci.

Antimicrobial Activity

Vancomycin has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

Aerobic Gram-Positive Bacteria

Corynebacterium spp.

Enterococcus spp. (including *Enterococcus faecalis*)

Staphylococcus aureus (including methicillin-resistant and methicillin-susceptible isolates)

Coagulase negative staphylococci (including *S.epidermidis* and methicillin-resistant isolates)

Streptococcus gallolyticus (previously known as *Streptococcus bovis*)

Viridans group streptococci

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

At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for vancomycin against isolates of similar genus or organism group. However, the efficacy of vancomycin in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Bacteria

Listeria monocytogenes

Streptococcus pyogenes

Streptococcus pneumoniae

Streptococcus agalactiae

Anaerobic Gram-Positive Bacteria

Actinomyces species

Lactobacillus species

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/ STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

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

15 REFERENCES

1. Byrd RA., Gries CL, Buening M.: Developmental Toxicology Studies of Vancomycin Hydrochloride Administered Intravenously to Rats and Rabbits. Fundam Appl Toxicol 1994; 23: 590-597.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Vancomycin Injection, USP is supplied as a ready to use clear, colorless to light brown solution in single-dose flexible bags containing 500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g and 2 g vancomycin in 100 mL, 150 mL, 200 mL, 250 mL, 300 mL, 350 mL and 400 mL of liquid (consists of water and PEG together with the excipients NADA and lysine) *[see Description (11)]*. The flexible bags are supplied in sealed aluminum overpouches. The bags are supplied in the following packages:

NDC number	Packaging configuration
70594-041-02	Carton of six 500 mg/100 mL bags
70594-041-03	Carton of twelve 500 mg/100 mL bags
70594-056-02	Carton of six 750 mg/150 mL bags
70594-056-03	Carton of twelve 750 mg/150 mL bags
70594-042-02	Carton of six 1 g/200 mL bags
70594-042-03	Carton of twelve 1 g/200 mL bags
70594-057-02	Carton of six 1.25 g/250 mL bags
70594-043-02	Carton of six 1.5 g/300 mL bags
70594-058-02	Carton of six 1.75 g/350 mL bags
70594-044-02	Carton of six 2 g/400 mL bags

16.2 Storage

Store below 25°C (77ºF), in original package. Product should be used within 28 days of removal from aluminum overpouch.

17 PATIENT COUNSELING INFORMATION

Risk of Embryo-Fetal Toxicity

Advise patients to notify their healthcare provider if they are pregnant prior to treatment with this formulation of vancomycin.

Infusion Reactions During or After Intravenous Use

Advise patients that generalized skin redness, skin rash, itching, flushing, muscle pain, chest pain, shortness of breath, wheezing, or dizziness may occur during Vancomycin Injection, USP infusion. These reactions can be lessened or prevented by infusing the drug over at least 60 minutes.

Acute Kidney Injury

Advise patients that Vancomycin Injection, USP can result in kidney damage and that blood tests are required to monitor vancomycin blood levels and kidney function during therapy.

Hearing Loss or Balance Problems

Advise patients that Vancomycin Injection, USP may result in decreased hearing and to report hearing loss or balance problems to their health care provider.

Antibacterial Resistance

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 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 or other antibacterial drugs in the future.

Diarrhea

Diarrhea is a common problem caused by antibacterial drugs, including vancomycin, which usually ends when the antibacterial drug is discontinued. Sometimes after starting treatment with antibacterial drugs, 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 antibacterial drug. If this occurs, patients should contact their physician as soon as possible.

xellia PHARMACEUTICALS

Manufactured for:
Xellia Pharmaceuticals USA, LLC
Buffalo Grove, IL 60089
Made in Switzerland

A company owned by Nova Holdings A/S.

 XEL-92