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Comparison of Vanco Ready® Vancomycin Injection Premix with Lyophilized Vancomycin Products in a Simulated Compounding & Clinical Setting

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Abstract: This study aimed to compare Xellia Pharmaceuticals' Vanco Ready® Vancomycin Injection, a premix, room-temperature stable vancomycin IV formulation, with compounded lyophilized vancomycin in a simulated sterile compounding setting, to assess dispensing time and dosing accuracy. Twelve simulations were performed to compare Vanco Ready® Vancomycin Injection premix, room-temperature formulation to single-dose, immediate-use compounded IV vancomycin and to multi-dose, batch compounded IV vancomycin. The first part of the study involved assessing the total dispensing time (i.e., time Rx order is received to when product is available for administration), which also included the compounding time required for the single-dose and batch-compounded, lyophilized products. The second component of the study involved measuring dosing accuracy, a composite of the diluent volumes needed for reconstitution and the residual drug volumes remaining in the vials, after the prescribed dose was removed. Vanco Ready® Vancomycin Injection premix was statistically better than single-dose, immediate-use compounded product and batch-compounded product for both dispensing time and dosing accuracy ($p<0.05$). The total dispensing time for Vanco Ready® Vancomycin Injection premix was an average of 1 minute/37 seconds compared to the total dispensing time for the single-dose, immediate-use compounded product, 20 minutes/28 seconds, and the batch-compounded product (8 bags) 28 minutes/7 seconds (average of 3 minutes/17 seconds per bag), which were inclusive of product verification and compounding times. Based on the total dispensing time, there was a statistical difference ($p<0.05$) between the total dispensing time for Vanco Ready® compared to single-dose, immediate-use compounded product, and compared to the batch compounded product average. The dose accuracy for Vanco Ready® Vancomycin Injection premix was assumed to be 100%, due to the rigorous, quality controls in place for commercially manufactured premix medications. The dosing accuracy of the single-dose, immediate-use compounded product was 91.20% and the dosing accuracy of batch-compounded product was 84.32%. Based on the dosing accuracy, there was a statistical difference ($p<0.05$) between the overall dose accuracy for Vanco Ready® compared to single-dose, immediate-use compounded product, and compared to the batch compounded product average. Vanco Ready® Vancomycin Injection premix showed a statistical improvement in the total dispensing time and dosing accuracy when compared to single-dose, immediate-use compounded product and batch compounded product. The results of this study indicate that commercially manufactured Vanco Ready® Vancomycin Injection may be a viable alternative over pharmacy compounded, lyophilized vancomycin, for healthcare institutions to consider for non-pregnant patients.

Keywords: Clinical Simulation, Compounding, Dispensing Time, Dose Accuracy, Error Reduction, Vanco Ready® Vancomycin Injection, Premix, Ready-to-Use

1. Introduction

The safety and efficacy of medications are at the center of medical decisions made by clinicians in critical life-threatening situations. Studies have shown that ~48% of errors involving intravenous medication usage were due to the steps required in preparation and use [1, 2]. The Anesthesia Patient Safety Foundation (APSF), American Society of Health System Pharmacists (ASHP), and the Institution for Safe Medication Practices (ISMP) all recommend that steps should be taken to reduce the risk of errors to patients to allow for more successful outcomes [3–5].

The objective of this study was to validate and compare Xellia Pharmaceutical's Vanco Ready® Vancomycin Injection, premix, with compounded lyophilized vancomycin in a simulated sterile compounding and clinical setting. Vancomycin is an antibiotic commonly used to treat critical infections which can lead to sepsis, a life-threatening organ dysfunction caused by a dysregulated host response, which has a 7.6% increase in mortality with every hour of delayed treatment [6]. Vancomycin is commonly made by reconstituting lyophilized powder for use in immediate use compounding and batch compounding. These products are either used immediately or require storage in a refrigerator due to a shorter beyond use date in accordance with USP <797> [7]. Vanco Ready® Vancomycin Injection is the first commercially available, room temperature stable, premix vancomycin formulation for immediate use, as it can be stored in automated dispensing cabinets [8]. This formulation requires no thawing or reconstitution and can be administered with no need to rely on personnel to compound or activate.

Dispensing time and dosing accuracy can be determined using a scenario-based evaluation. In this research study, the scenario compared compounding parameters between an available lyophilized vancomycin formulation and Vanco Ready® Vancomycin Injection premix bags in a simulated sterile compounding environment and clinical setting. Vancomycin 1g and 10g vials were used to compound IV vancomycin bags at a dose of 1.25g/250mL. Vanco Ready® was dispensed in the same dose and concentration but did not require sterile compounding as it's available in a sterile, ready to use final dosage form. Simulations were conducted in a compounding cleanroom and patient bedside setting using the Medical College of Wisconsin (MCW) sterile compounding lab and the Standardized Teaching Assessment Resource (STAR) center in a similar manor to that of previously executed clinical simulation studies conducted [9].

In the clinical setting, patients require a thorough health work up to evaluate drug-drug interactions and contraindications for use. The simulations performed in this study were based on the best-case scenario where the patient has no drug interactions or contraindications. This consideration allowed each formulation to be evaluated equally. Due to Vanco Ready® Vancomycin Injection's black box warning (Figure 1), use in patients that are in their first or second trimester of pregnancy is not allowed due to reproduction concerns [8, 10].

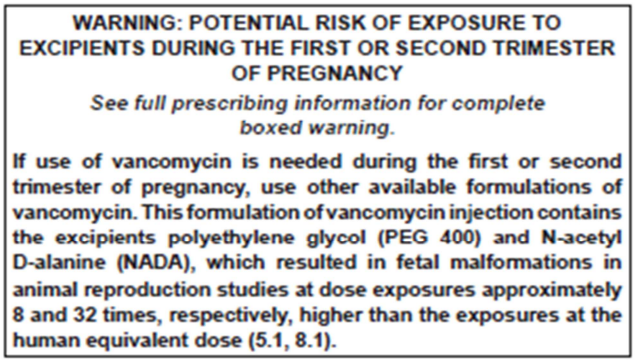

Figure 1. *Vanco Ready® Vancomycin Injection's Black Box Warning.*

During this study, commercially manufactured Vanco Ready® Vancomycin Injection was compared with an available lyophilized vancomycin preparation based on the following parameters:

1) Dispensing Time: Efficiency of use/reduction of time included:
   a) Total dispensing time: Time from prescription order received to hanging of IV bag
   b) Compounding Time: Time taken to compound and verify one IV bag (via single dose compounding and batch compounding)
2) Dosing Accuracy: Error reduction/accuracy of medication dosing - Composite of reconstitution volume and residual volume.

2. Materials and Methods

This study was conducted at the Medical College of Wisconsin (MCW) located in Milwaukee, WI. Investigators from the MCW School of Pharmacy and Froedtert Hospital (FH) teamed up to perform the simulations. The STAR Center and the sterile compounding lab at MCW provide a controlled environment where students, residents, physicians, pharmacists, nurses, and other healthcare professionals can practice their clinical and compounding skills using standardized (or actor) patients, medical simulators, and task trainers under the direction of MCW faculty and staff. In this study we first utilized the simulated cleanroom environment for compounding and then transitioned into the STAR center as the simulated patient room. Vanco Ready® Vancomycin Injection was provided by Xellia Pharmaceuticals USA, LLC, and the lyophilized vancomycin powder and ancillary supplies were procured from MCW and FH. The study was approved by the MCW/FH Institutional Review Board (PRO00040794). Financial support to conduct the study was also provided by Xellia Pharmaceuticals USA, LLC.

The following objectives were assessed for Vanco Ready® Vancomycin Injection premix, single-dose, immediate-use compounded vancomycin and batch compounded

vancomycin:

Dispensing Time: Time was measured from the start of the experiment (order placed) to the time taken to handover the IV bags to the clinician for administration. The time captured represented the Dispensing Time, which also included the time required for compounding. A reduction in compounding time was seen as repetition by the participants led to more efficient compounding due to their familiarity. Compounding time was analyzed based on the time required to compound and verify one bag of lyophilized vancomycin, as both a single-dose, immediate-use and a batch compounded product.

Dosing Accuracy: A composite of the volume required to reconstitute each vial, and the residual volume (volume remaining in vial after removing required dose), were measured in a controlled setting to define the baseline volumes. Once the volumes were measured, an absolute percent error could be calculated.

2.1. Clinical Setting

Generally, FH department of pharmacy technicians prepare vancomycin by batch compounding large quantities of bags which are then stored in the refrigerator until an order is received. In rare instances, a single bag may need to be prepared for immediate use.

An immediate-use compounded formulation of one 1.25g/250mL IV bag of vancomycin requires two 1g vials, each needing 20 mL of sterile water to reconstitute. One vial would require the full 20 mL reconstituted volume to be withdrawn and added to a 250 mL IV bag of 0.9% sodium chloride (NS), and the other 1 g vial would require 5mL of the reconstituted volume to be withdrawn and added to the bag of NS. Before addition of vancomycin, 25mL of NS are removed from the 250mL diluent bag per FH procedure. Originally, the protocol for this experiment called for the immediate-use compounding group to use a 1g vial and a 500mg vial to prepare the final formulation. However, due to a back order, the 500mg vials were unavailable requiring the use of the second 1g vial.

Batch-compounded vancomycin used one 10 g vial of vancomycin requiring reconstitution with 95 mL of sterile water. A participant then withdraws 12.5 mL of the reconstituted solution and adds this directly to each of the eight 250 mL bags of NS, making 8 total bags. The batch-compounded bags did not require any volume to be removed from the 250 mL diluent bags because the added reconstituted volume was more concentrated and would be within 10% of the 250 mL IV bag (within hospital's acceptable margins). The batch-compounded bags are made utilizing a vented transfer pin within the vial that allows for easier drug removal, negating pressure gradients and the need to puncture the vial more than once. As USP 797 guidelines are followed in most institutions, these same guidelines were also followed for this study [7]. With consultations of FH pharmacists, our process was validated and determined to be indicative of compounding procedures seen within other major health systems and consistent with the product label directions for use.

2.2. Pre-Simulation Preparation

An indirect measure was used to assess the dose accuracy by measuring the reconstitution volume and residual volume in the vials. Reconstitution volume is the measure of solvent added to dissolve the lyophilized powder. Participants marked the meniscus after adding solvent, which was used as an indicator of accuracy of the volume of solvent added. Similarly, the residual volume remaining in the vial was measured post simulation as another indicator of accuracy. Volumes were measured by using Falcon® Brand serological pipettes with an accuracy of 5 ± 0.1 mL. A new pipette was used for each measure.

Baseline values were measured in the controlled setting before the simulation. Three, 10g vials of vancomycin and six, 1g vials of vancomycin were reconstituted as previously mentioned. These vials were then marked at the bottom of the meniscus line. After being marked, the three 10g vials had 12.5mL removed 8 times from each multi-dose vial, the three 1g vials had 20mL removed from each, and three 1g vials had 5mL removed from each. The residual volumes were measured and used as the baseline for the expected residual volumes to be present after participants formulated and prepared their final drug product. After the residual volumes were determined, the vials were then filled to the marked meniscus line. This volume was measured and used as an indirect measurement of the reconstitution volume. Averages were taken for each measure and used as the baseline measurements for accuracy comparison. These accuracy values were then used to determine the overall dosing accuracy. The baseline measurements were used as the comparator to calculate the dosing accuracy from the simulations.

To further understand the overall compounding time on a per bag basis, time to hand wash, gown and garb was also recorded. The time to hand wash, gown and garb was performed six times before the simulations. The average time taken was two minutes.

2.3. Room Setting and Personnel

Personnel with healthcare backgrounds were used for this study. The participants were educated about the compounding simulation activity beforehand and allowed to conduct practice simulations in advance to orient them to the space and procedures. Six students volunteered and consented for three compounding roles, and three students were selected based upon compounding experience. The three compounders were designated as α, β, and π to allow their data to be associated to the correct simulation and recording sheets.

These three participants were assigned at the start of each simulation and would rotate after conclusion of each simulation and hence each participant would prepare all three preparation methods over the course of three simulations. Each participant had access to a pharmacy supply cart placed in the Sterile Products Lab (referred to as participants for the

simulation portion of this experiment) to prepare the associated formulations. To simulate real life scenarios, the carts were stocked with look-a-like-sound-a-like (LASA) medications (e.g. Valacyclovir) along with several other common compounding drug cart medications. Carts were resupplied after each simulation.

2.4. Simulation Experiments

Participants performed six simulations each day (each participant performed each preparation method twice), resulting in an initial six data points for each preparation method. Participants returned on a different day to evaluate inter-day variations. This design allowed for six additional data points for each preparation method, resulting in a total of 12 data points for each preparation method. Based on previous experience, this was a proper sample size to detect a statistically significant difference in the time required to dispense (compound and verify) the product [4]. The expected total dispensing time required for Vanco Ready® was assumed to be 30 secs, immediate use compounding at 20 min, and batch compounding at 30 minutes for 8 bags (~3.5-4 minutes per bag). Due to this large variation between Vanco Ready® and other formulations, a power analysis was not necessary.

For the simulation experiment, a pharmacist would announce an order for vancomycin at a fixed dose of 1.25g/250mL to initiate each simulation. The pharmacist would then begin three stopwatches to record the time. All participants were required to identify and collect the necessary supplies for their preparation method. If participants were assigned to the immediate-use compounding or batch compounding, then supplies required cleaning and placement through a passthrough into the sterile lab. Hand washing, gowning, garbing, and then compounding were also required. Each product was prepared in the same manner as previously mentioned in the clinical setting section. Participants would mark the meniscus line after the vial reconstitution to be assessed after the simulations were concluded. The immediate-use compounding and batch compounding groups would label each finished product then place the finished product back in the passthrough and exit the sterile room. Vanco Ready® did not require compounding and was prepared by removing the product from the foil overwrap.

The pharmacist would verify the final products and record the time on the stopwatch as the time to verify (which also included time to compound). All bags in the batch compounding group had to be verified at the same time before going to the STAR Center. The stopwatch and one bag of vancomycin were given to the participant to walk to the STAR center where the IV bag would be hung. After hanging the bag, the participant would stop the stopwatch and have the time recorded (total dispensing time). The encounters in the STAR center and sterile lab were videotaped, to be reviewed as necessary. Notes were taken throughout the simulations by the observer and lead investigators. Collected vials were measured for dosing accuracy.

3. Results and Discussion

Vanco Ready® Vancomycin Injection, immediate-use compounded vancomycin and batch compounded vancomycin formulations were compared against each other in a simulated clinical setting; assessing dispensing time and dosing accuracy. Data was analyzed for inter-day variations and medication errors. A two-tail t-test was used for statistical analysis comparing Vanco Ready® to immediate-use compounding, and Vanco Ready® to batch compounding preparations.

3.1. Dispensing Time (Efficiency of Use)

Dispensing time is an indicator for efficiency of use in the clinical setting. It was calculated by using the total time taken from order placement until administration. A subset of dispensing time, compounding time, was also calculated to determine the time required to sterile compound the products. Although both time parameters would provide similar trends, total dispensing time provides a more complete view of product movement through a facility.

3.1.1. Compounding Time

The compounding time for Vanco Ready®, was considered zero as the product does not require any compounding, being a premix IV bag. However, time for verification as part of the total dispensing time was captured instead for Vanco Ready®. Compounding times for immediate-use and batch compounding were determined based on the time required to compound a single bag. The time taken to prepare one bag was determined based on a best-case scenario where a technician was always in the sterile environment, and as such, excluded time related to gathering supplies, hand washing, gowning, and garbing. Consequently, a time of 120 seconds, was removed from all the compounding times. The time to compound a single bag for immediate-use was 17 minutes and 30 seconds (± 1 minute 56 seconds) and to batch compound was 3 minutes and 17 seconds (± 14 seconds), which represents an average compounding time for a single bag within the batch. (Figure 2). T-tests showed a significant reduction in the time for verification of Vanco Ready® compared to compounding immediate-use compounded vancomycin ($p < 0.05$), and compounding batch compounded vancomycin ($p < 0.05$). The time to compound a single dose, immediate-use product showed greater standard deviations compared to the total dispensing time of Vanco Ready®, meaning there is high variability in the process to prepare a single dose immediate-use product for a patient. Batch compounding is more common in the clinical setting for high volume products, as such these results indicate a clinically significant savings in tech hours when vancomycin is batch compounded compared to immediate-use compounded, allowing time allocation to other needed tasks.

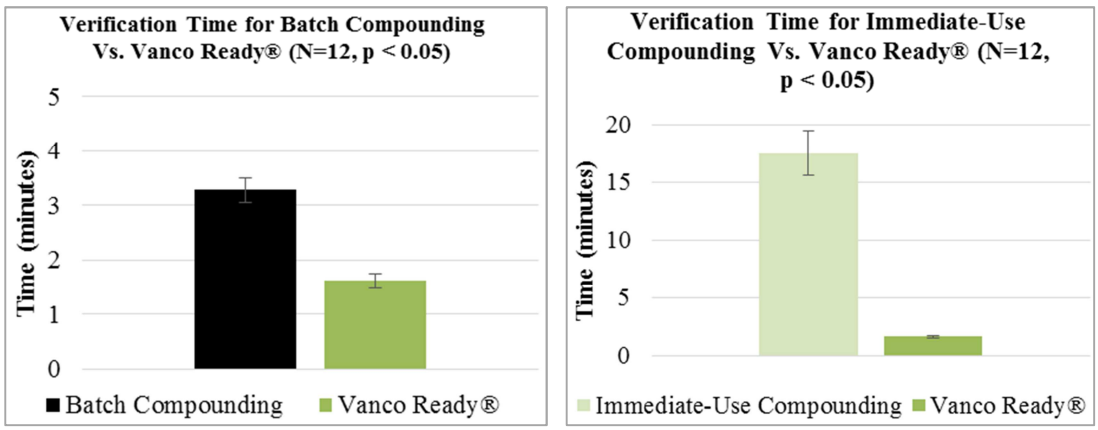

Figure 2. *Verification Time of Vanco Ready® vs. Batch Compounding (per bag average) and Verification Time of Vanco Ready® vs. Immediate-use Compounding.*

3.1.2. Total Dispensing Time

The total time taken to dispense a dose to the patient's bedside was 1 minute and 37 seconds (± 9 seconds), for Vanco Ready®, 20 minutes and 28 seconds (± 1 minute 54 seconds) for immediate-use, and 28 minutes and 7 seconds (± 4 minutes and 20 seconds) for batch compounding (average of 3 min and 17 sec/bag). (Figure 3). Total dispensing time for batch compounding needed to include the time to compound the entire batch, as a single dose cannot be verified during the batching process. There was a larger standard deviation for the immediate-use compounded products and batch compounded products compared to Vanco Ready®, with immediate-use compounding having the largest standard deviation. In a real-life setting, Vanco Ready® can be placed in an automated dispensing cabinet as it can be stored at room temperature. If a batch or immediate-use vancomycin bag were prepared in a sterile IV room, then the bags would be stable for 4 days at room temperature and 10 days when refrigerated per USP <797> [7]. If a bag was compounded in a non-sterile preparation area, then it would only be stable for 12 hours.

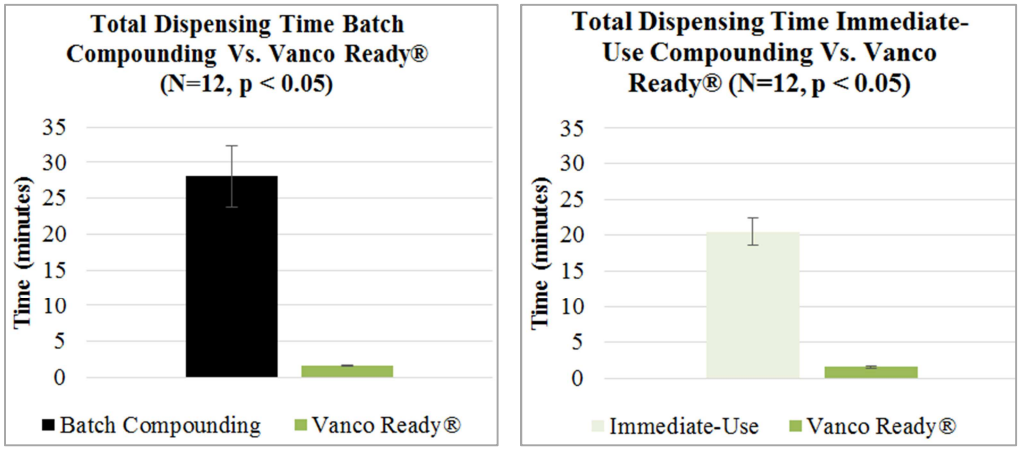

Figure 3. *Total dispensing time of Vanco Ready® vs. Batch Compounding (all bags) and Total dispensing time of Vanco Ready® vs. Immediate-Use Compounding.*

3.2. Dosing Accuracy

Accuracy of dosing was indirectly evaluated by measuring the volumes used to reconstitute a vial and the volumes of residual vancomycin solution left in the vial after making the finished products.

Vanco Ready® dosing accuracy was assumed to be 100% due to its commercial manufacturing. Immediate-use compounding had a reconstitution volume accuracy of 98.58% (± 0.77%), a residual volume accuracy of 83.82% (± 11.11%) and a composite volume accuracy of 91.20%. Residual volume variations of immediate-use compounding can be attributed to the need for requiring 2 vials for dosing. Batch compounding had a reconstitution volume accuracy of 95.06% (± 10.16%), a residual volume accuracy of 73.57% (± 18.09%), and a composite volume accuracy of 84.32% for each IV bag. Reconstitution volumes and residual volumes were used to form composite volumes, which determined the dosing accuracy for all compounded products (Figure 4). There was a statistical difference ($p<0.05$) in both the dosing accuracy for batch-compounding vs. Vanco Ready® and immediate-use compounding vs. Vanco Ready®.

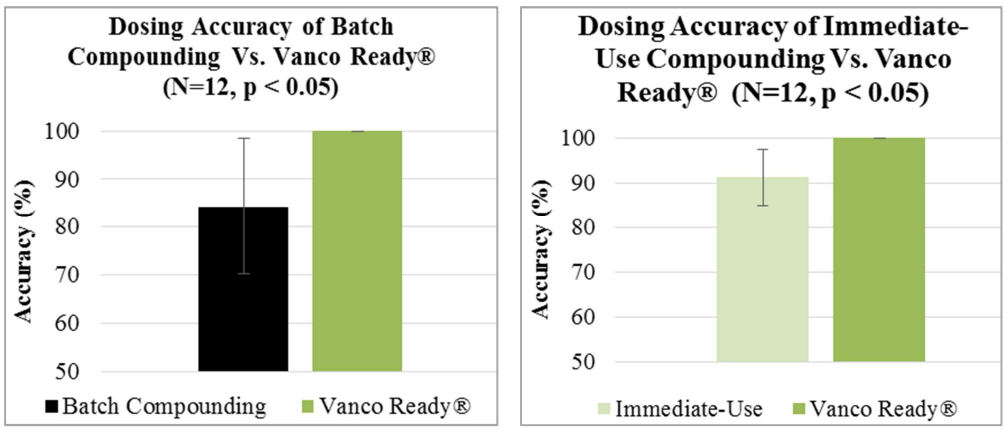

Figure 4. *Dosing Accuracy of Batch Compounding (per bag average) versus Vanco Ready® and dosing accuracy of Immediate-Use Compounding versus Vanco Ready®.*

3.3. Medication Errors

One major error observed in this study occurred when a technician failed to compound the 8th bag in the batch-compounding arm, as he did not have enough vancomycin to complete the full batch. The residual volume data indicated that additional vancomycin had been added to the other 7 bags, inadvertently increasing the dose/concentration of those bags. As well, some drug volume may have been lost due to the multiple manipulations that occurred while compounding the batch.

The possibility of inadvertent administration of Vanco Ready® premix to patients in the first or second trimester of pregnancy is beyond the scope of this study but should be considered by the clinician to ensure safe product administration.

3.4. Inter-Day Variations

Inter-day variations were analyzed for each arm of the study, for the various parameters. Related to time measurement, there was no statistically significant difference in the total dispensing time for Vanco Ready® ($p=0.62$), immediate-use compounding ($p=0.15$) or batch compounding ($p=0.87$) among the different days. As well, there was not a statistically significant inter-day difference in the compounding times with batch-compounding ($p=0.30$) or with immediate-use compounding ($p=0.31$).

However, an inter-day variation did occur with the verification times for the premix Vanco Ready® product as Vanco Ready® showed a significantly faster total dispensing time on the second day of the simulation compared to day one ($p<0.05$). It was thought that this variability could be due to increased participant performance in verification times that occurred during the study.

4. Conclusion

During this clinical simulation study, Vanco Ready® Vancomycin Injection showed significantly better dispensing time and dosing accuracy compared to lyophilized vancomycin for immediate-use compounding and batch compounding. Vanco Ready® took less time to verify and dispense compared to lyophilized vancomycin, as it did not require sterile compounding. Dosing accuracy, which was measured as a composite based on reconstitution volume and residual drug volume, was significantly better for premix Vanco Ready® compared to immediate-use and batch compounded vancomycin. This data suggests that use of Vanco Ready® may result in less medication errors in the clinical setting, related to vancomycin dosing. However, this simulation did not factor in clinical simulations involving patients with drug-drug interactions or contraindications. Clinical considerations for the usage of Vanco Ready® require a full patient work up, as the black box warning for Vanco Ready® warns that pregnant patients in the first or second trimester should receive another vancomycin formulation due to the potential fetal malformations caused by the excipients polyethylene glycol (PEG 400) and N-acetyl D-alanine (NADA)[3]. This study began assuming the drug utilization review was properly conducted.

Since every healthcare facility has its own procedures on how to sterile compound lyophilized medications, variability occurring in the compounding process is inevitable. Vanco Ready® can decrease this variability by providing a more consistent, commercially manufactured, room temperature stable product. The results of this study show that Vanco Ready® Vancomycin Injection, when used in the approved patient population, could be a valuable option for institutions currently compounding lyophilized vancomycin, with limited pharmacy personnel or facilities to compound sterile products.

Acknowledgements

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

RECENT MAJOR CHANGES

Boxed Warning	10/2021
Warnings and Precautions, Severe Dermatologic Reactions (5.5)	5/2021
Warnings and Precautions, Potential Risk of Exposure to Excipients During the First or Second Trimester of Pregnancy (5.1)	10/2021

WARNING: POTENTIAL RISK OF EXPOSURE TO EXCIPIENTS DURING THE FIRST OR SECOND TRIMESTER OF PREGNANCY

See full prescribing information for complete boxed warning.

If use of vancomycin is needed during the first or second trimester of pregnancy, use other available formulations of vancomycin. This formulation of vancomycin injection contains the excipients polyethylene glycol (PEG 400) and N-acetyl D-alanine (NADA), which resulted in fetal malformations in animal reproduction studies at dose exposures approximately 8 and 32 times, respectively, higher than the exposures at the human equivalent dose (5.1, 8.1).

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)

DOSAGE AND ADMINISTRATION

- Obtain a pregnancy test in females of reproductive potential prior to initiating treatment with Vancomycin Injection. *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1,8.3)]*
- 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, 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 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)
- Severe Dermatologic Reactions: Discontinue Vancomycin Injection at the first appearance of skin rashes, mucosal lesions, or blisters. (5.5)
- *Clostridioides difficile*-Associated Diarrhea: Evaluate patients if diarrhea occurs. (5.6)
- Neutropenia: Periodically monitor leukocyte count. (5.8)
- Phlebitis: To reduce the risk of local irritation and phlebitis administer Vancomycin Injection by a secure intravenous route of administration. (5.9)
- 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. (5.10)

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)

See 17 for patient counselling information.

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