

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209481Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 29, 2018

Requesting Office or Division: The Division of Anti-Infective Products (DAIP)

Application Type and Number: NDA 209481

Product Name and Strength: Vancomycin Hydrochloride for Injection, USP;
250 mg/vial, 750 mg/vial, 1.25 g/vial, and 1.5 g/ vial

Applicant/Sponsor Name: Mylan

FDA Received Date: June 22, 2018

OSE RCM #: 2016-1667-1

DMEPA Safety Evaluator: Sevan Kolejian, PharmD, MBA

DMEPA Team Leader: Otto L. Townsend , PharmD

1 PURPOSE OF MEMORANDUM

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling for Vancomycin Hydrochloride for Injection; 250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.5 g/vial (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label and carton labeling for Vancomycin Hydrochloride for Injection; 250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.5 g/vial are acceptable from a medication error perspective.

We have no further recommendations at this time.

^a Kolejian, S. Label and Labeling Review for Vancomycin for injection (NDA 209481). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 9. RCM No.: 2016-1667.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JUNE 22, 2018.

A.1 Label and Labeling Images

Container label and Carton labeling: View EDR section 1.14.2.1

<\\cdsesub1\evsprod\nda209481\0019\m1\us\114-labeling\final\carton-or-container\final-carton-andor-container-label.pdf>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OTTO L TOWNSEND on behalf of SEVAN H KOLEJIAN
06/29/2018

OTTO L TOWNSEND
06/29/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 13, 2018

To: Alma Davidson, M.D.
Division of Anti-Infective Products (DAIP)

Deepak Aggarwal, Regulatory Project Manager, (DAIP)

Abimbola Adebowale, (DAIP)

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for Vancomycin for Injection

NDA: 209481

In response to DAIP consult request dated December 18, 2017, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Vancomycin for Injection.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP on March 5, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 10, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID F FOSS
03/13/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 9, 2018
Requesting Office or Division:	The Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 209481
Product Name and Strength:	Vancomycin Hydrochloride for Injection, USP; 250 mg/vial, 750 mg/vial, 1.25 g/vial, and 1.5 g/ vial
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Mylan
Submission Date:	October 10, 2017
OSE RCM #:	2016-1667
DMEPA Primary Reviewer:	Sevan Kolejian, PharmD, MBA
DMEPA Team Leader:	Otto L. Townsend , PharmD

1 REASON FOR REVIEW

As part of the NDA approval process for Vancomycin Hydrochloride for Injection; 250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.5 g/vial, the Division of Anti-Infective Products (DAIP) requested that we review the proposed container label, carton labeling, and prescribing information (PI) to determine if they are acceptable from a medication error perspective.

1.1 REGULATORY HISTORY

The Application received a Complete Response (CR) on May 19, 2017 due to an unfavorable facilities inspection. In the CR letter, the Agency noted that the Applicant previously proposed (b) (4)

Additionally, as requested by the Agency in the CR letter, the revised labeling has been prepared pursuant to the most recently approved labeling for the Reference product.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Vancomycin for injection is currently available from various manufacturers as 500 mg, 750 mg, and 1 g strength vials. Vancomycin is also available as pharmacy bulk packages of 5 g, and 10 g vials. We note that Mylan currently markets Vancomycin for injection under ANDA 065397 in the same strengths listed above except for the 750 mg strength.

We note that Vancomycin for Injection is approved for neonatal, pediatric and adult populations. We note that the dosing is highly individualized, and based on patient’s pharmacokinetics parameters, weight (mg/kg) and clinical indication (goal trough). The proposed new strengths (250 mg, 1.25 g and 1.5 g) will support the variable dosages of Vancomycin that are already prepared in practice to meet the individual patient’s dosing need. Hence, we have no safety concerns with the introduction of new strengths for Vancomycin Hydrochloride for Injection into the market. Additionally, the proposed container labels and carton labeling for the new strengths are well differentiated from the vancomycin products currently marketed because Mylan is using different color design for each strength presentation. The strengths appear prominently on the proposed container labels and carton labeling, which would help to differentiate between the strengths. (b) (4)

We performed a risk assessment of the proposed container label, carton labeling, and prescribing information for Vancomycin Hydrochloride for Injection to identify deficiencies that may lead to medication errors and to identify areas that could be improved. Our review of the PI, the container labels and carton labeling identified areas that could be improved to increase clarity, consistency and readability of important information. In section 4.1 and 4.2, we provide recommendations.

4 CONCLUSION & RECOMMENDATIONS

We have no safety concerns with the introduction of additional strengths for Vancomycin Hydrochloride for Injection (250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.5 g/vial). The proposed labels and labeling can be improved to increase clarity and prominence of important information to promote safe use of this product (See section 4.1 and section 4.2).

If you have further questions or need clarifications, please contact Janet Higgins, OSE Project Manager, at 240-402-0330.

4.1 RECOMMENDATIONS FOR THE DIVISION

We advise the following recommendations be implemented prior to approval:

A. Dosage and Administration - *Section 2.4, Preparation* (b) (4)

- a. To improve clarity and to prevent the risk of errors in the preparation of Vancomycin Hydrochloride for Injection, add the statements: "Vancomycin must be reconstituted and further diluted" and "Then further dilute in a suitable infusion solution to a final concentration of 5 mg/ml (see following table for volume of infusion solution) and administer over a period of at least 60 minutes". Also, add a title to the table, clarify the table headings, and add a column to include the further dilution information incorporating the information about the further dilution diluent volume and storage in table. As an illustration,, we provided the screenshot of the proposed revisions for your consideration as follow:

2.4 Preparation (b) (4)

Vancomycin must be reconstituted and further diluted. At the time of use, reconstitute the vials of Vancomycin Hydrochloride for Injection with Sterile Water for Injection to a concentration of 50 mg of vancomycin/mL (see (b) (4) table for volume (b) (4)). Then further dilute in a suitable infusion solution to final concentration of 5 mg/ml (see following table for volume of infusion solution) and administer over a period of at least 60 minutes.

Table: Volume of Diluent to Add for Reconstitution and Further Dilution

<u>Vancomycin Strength</u> (b) (4) Vial	<u>Volume of Sterile Water for Injection for reconstitution</u> ^a (b) (4)	<u>Volume of infusion solution^b to further dilute to a final concentration of 5 mg/mL</u>
250 mg	5 mL	<u>50 mL</u>
750 mg	15 mL	<u>150 mL</u>
1.25 g	25 mL	<u>250 mL</u>
1.5 g	30 mL	<u>300 mL</u>

^a After reconstitution, the vials may be stored in a refrigerator for (b) (4) without significant loss of potency.

^b See section 2.3 for the list of the compatible infusion solutions.

~~The desired dose diluted in this manner should be administered by intermittent IV infusion over a period of at least 60 minutes.~~

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

4.2 RECOMMENDATIONS FOR MYLAN

We recommend the following be implemented prior to approval of this NDA 209481:

A. Container Label

1. Revise the usual Adult dosage statement to read "See Package Insert" because the dose is variable and patient specific.
2. We note that the package type term "Single dose" is used in the PI; however, is not noted on the container label and carton labeling. Add the package type term and ensure that the package type term is consistent throughout labels and labeling.

B. Carton Labeling

1. See A.1 above.
2. See A.2 above.
3. For clarity and consistency, revise the statement, (b) (4) on the side panel to read "Reconstitute contents with XX mL Sterile Water for Injection".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vancomycin for Injection, USP that Mylan submitted on July 20, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Vancomycin Hydrochloride for Injection and the Listed Drug		
Product Name	Vancomycin Hydrochloride for Injection, USP	Listed Drug Vancomycin Hydrochloride for Injection, USP, ANDA 060180
Initial Approval Date	N/A	11/06/1964
Active Ingredient	Vancomycin	
Indication	<p>(b) (4)</p> <ul style="list-style-type: none"> treatment of (b) (4) septicemia, bone infections, lower respiratory tract infections, skin and skin structure infections 	<ul style="list-style-type: none"> treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (β-lactam-resistant) staphylococci treatment of staphylococcal endocarditis including septicemia, bone infections, lower respiratory tract infections, skin and skin structure infections antibiotic-associated pseudomembranous colitis staphylococcal enterocolitis
Route of Administration	Intravenous infusion	Intravenous infusion Oral administration
Dosage Form	For injection	
Strength	250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.5 g/vial	500 mg/vial, 1 g/vial, 10 g/vial

Dose and Frequency	<ul style="list-style-type: none"> • <i>Adults:</i> The usual daily intravenous dose is 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours. • <i>Pediatric Patients:</i> The usual intravenous dosage of vancomycin is 10 mg/kg per dose given every 6 hours. • <i>Neonates:</i> In pediatric patients up to the age of 1 month, the total daily intravenous dosage may be lower. In neonates, an initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the 1st week of life and every 8 hours thereafter up to the age of 1 month. 	
How Supplied	<p>Vancomycin Hydrochloride for Injection, USP equivalent to 250 mg vancomycin in a 5 mL flip top vial with an ash gray seal, (b) (4)</p> <p>Vancomycin Hydrochloride for Injection, USP equivalent to 750 mg vancomycin in a 20 mL flip top vial with an ash gray seal in packages of 10 vials.</p> <p>Vancomycin Hydrochloride for Injection, USP equivalent to 1.25 g vancomycin in a 30 mL flip top vial with an ash gray seal, (b) (4)</p> <p>Vancomycin Hydrochloride for Injection, USP equivalent to 1.5 g vancomycin in a 30 mL flip top vial with a golden brown seal, (b) (4)</p>	<p>Vancocin® HCl (Vancomycin Hydrochloride for Injection USP) are available in:</p> <p>The 500 mg,* 10-mL vials are available as: 10-mL vials and Pack of 25</p> <p>The 1 g,* 20-mL vials are available as: Pack of 25</p> <p>Also available:</p> <p>Vancocin® HCl ADD-Vantage®† Vials (Vancomycin Hydrochloride for Injection USP) are available in:</p> <p>The 500 mg,* 15-mL vials are available as: Pack of 10</p> <p>The 1 g,* 15-mL vials are available as: Pack of 10</p> <p>Vancocin® HCl Pharmacy Bulk Package (Vancomycin Hydrochloride for Injection USP) are available in:</p> <p>The 10 g,* 100-mL vials are available as: 100-mL vial</p>
Storage	<p>Prior to reconstitution, store (b) (4) at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]</p>	<p>Prior to reconstitution, the vials may be stored at room temperature, 15° to 30°C (59° to 86°F).</p>
Container Closure	<p>Glass vial</p>	<p>Glass vial and Abbots ADD-Vantage vials</p>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 5, 2018, we searched DMEPA's previous reviews^{a,b} using the terms, Vancomycin. Our search identified two previous reviews related to this review. The first review was a memorandum documenting that we would not complete our review of the proposed labeling until the application is resubmitted and the identified deficiencies have been appropriately addressed. The second review was a postmarketing review related to packaging confusion between Mylan's Vecuronium and Vancomycin products. The review concluded that no regulatory action was needed because Mylan had recently revised its vecuronium container label.

^a Kolejjan, S. Labeling MEMORANDUM for Vancomycin Hydrochloride for Injection NDA 209481. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 17 RCM No.: 2016-1667.

^b Miller, C. Postmarket Medication Error Review for packaging confusion between Mylan's Vecuronium and Vancomycin products. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUN 16 RCM No.: 2016-2569.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Vancomycin Hydrochloride for Injection, USP labels and labeling submitted by Mylan on October 10, 2017.

- Container label
- Carton labeling

G.2 Label and Labeling Images

1. Container label and Carton labeling:

View EDR section 1.14.2.1

<\\cdsesub1\evsprod\nda209481\0009\m1\us\114-labeling\final\carton-or-container\final-carton-andor-container-label.pdf>

2. Prescribing Information (PI)

- Proposed draft PI View EDR section 1.14.2.2

<\\cdsesub1\evsprod\nda209481\0009\m1\us\114-labeling\final\package\final-package-insert.pdf>

- The tracked changes file for the proposed prescribing information View EDR

Section 1.14.2.3 <\\cdsesub1\evsprod\nda209481\0010\m1\us\114-labeling\final\labeling\final-labeling-text-track-changes-word.docx>

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SEVAN H KOLEJIAN
02/09/2018

OTTO L TOWNSEND
02/09/2018

LABELING MEMORANDUM

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 16, 2017
Requesting Office or Division:	The Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 209481
Product Name and Strength:	Vancomycin Hydrochloride for Injection, USP; 250 mg/ vial, 750 mg/vial , 1.25 g/vial and 1.5 g/ vial.
Product Type:	Single
Rx or OTC:	Rx
Applicant/Sponsor Name:	Mylan
Submission Date:	July 20, 2016
OSE RCM #:	2016-1667
DMEPA Primary Reviewer:	Sevan Kolejian, PharmD
DMEPA Team Leader:	Otto L. Townsend , PharmD

1 REASON FOR REVIEW

The Division of Anti-Infective Products (DAIP) requested that we review the proposed container label, carton labeling, and prescribing information for Vancomycin Hydrochloride for Injection, submitted under NDA 209481 to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

During the review cycle, DAIP determined the application could not be approved in its current form and DAIP has decided to issue a Complete Response; therefore, we will complete our Label and Labeling review when the application is resubmitted and the identified deficiencies have been appropriately addressed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SEVAN H KOLEJIAN
05/16/2017

OTTO L TOWNSEND
05/16/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 4-19-2017

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, M.D.
Director,
Division of Pediatric and Maternal Health

To: Division of Anti-Infective Products

Drug : Vancomycin hydrochloride for injection (b) (4); NDA 209481

Proposed Indications:

(b) (4)

- Treatment of (b) (4) septicemia, bone infections lower respiratory tract infections, skin and skin structure infections

(b) (4)

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Labeling as part of 505(b)(2) application

Applicant: Mylan

- Materials Reviewed:**
- Applicant's proposed labeling and pregnancy safety review
 - Literature review
 - Vancomycin hydrochloride for injection and oral capsule by Fresenius

Kabi approved labeling (reference listed drugs)

Consult Question: Please review the Pregnancy and Lactation Labeling Rule (PLLR) Labeling

INTRODUCTION

The applicant submitted a 505 (b) (2) NDA for Vancomycin hydrochloride for injection (b) (4) on October 28, 2016. The drug substance is different from the reference listed drugs (RLDs), due to different dosage strengths. The proposed indications, (b) (4) are the following:

(b) (4)

- treatment of (b) (4) septicemia, bone infections, lower respiratory tract infections, skin and skin structure infections

(b) (4)

The Division of Anti-Infective Products (DAIP) consulted the Division of Pediatric and Maternal Health (DPMH) on October 31, 2016, to assist with reviewing the Pregnancy and Lactation subsections of labeling.

BACKGROUND

Product Background

Vancomycin is a glycopeptide antibiotic that was first approved in 1964. Approved labeling for the RLD states that oral vancomycin is poorly absorbed. Vancomycin hydrochloride for injection is administered intravenously for systemic therapy and orally for intraluminal therapy of the gastrointestinal tract. The molecular weight is 1,485.71 Daltons. The half-life is 4 to 6 hours.

Current state of the labeling of Vancomycin hydrochloride for injection by Fresenius Kabi, the RLD

The currently approved labeling (2016) is in the Physician Labeling Rule format. The Pregnancy section is labeled category B and states that vancomycin was not teratogenic in rats given 1 time and rabbits given 1.1 times the maximum recommended human dose/day (based on body surface area). Labeling includes information from a published study of pregnant women who were administered vancomycin during the second and third trimesters whose infants did not have sensorineural hearing loss or nephrotoxicity.

The Nursing Mothers section includes a statement that vancomycin is excreted in human milk and that because of the potential for adverse events, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Clinical Guidelines that include vancomycin use in pregnancy

The Centers for Disease Control (CDC) guidelines on the prevention of perinatal group B streptococcus (GBS) disease recommend the use of vancomycin (1 g intravenously every 12

hours) for the treatment and prophylaxis of GBS in penicillin-allergic pregnant women at high risk for anaphylaxis if their isolate is intrinsically resistant to clindamycin as determined by antimicrobial susceptibility testing, if the isolate demonstrates inducible resistance to clindamycin, or if susceptibility to both agents is unknown.¹

Pregnancy and Lactation Labeling Rule (PLLR)

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,” also known as the Pregnancy and Lactation Labeling Rule (PLLR), took effect.² The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

Pregnancy

Nonclinical Experience

Vancomycin did not show adverse developmental effects in rats or rabbits at doses less than or equal to the recommended maximum human dose (based on body surface area). No additional nonclinical studies were conducted for this NDA. Please refer to the toxicology review by Dr. Wendelyn Schmidt.

Review of Human Pregnancy Data

Applicant’s literature review

The applicant reviewed published data on vancomycin use in pregnancy, described below.

Because vancomycin has been associated with sensorineural hearing loss and nephrotoxicity, a study evaluated fetal hearing loss and nephrotoxicity during pregnancy in women treated with vancomycin for suspected or documented methicillin-resistant staphylococcal aureus.³

Vancomycin (1 g intravenously every 12 hours) was administered to 10 intravenous drug-dependent patients for at least 1 week during their second and third trimesters, 10 non-intravenous drug-dependent patients received no treatment, and 10 untreated intravenous drug-dependent patients served as substance abuse controls. Auditory brainstem testing and renal function studies were performed in all neonates. There was one infant in the vancomycin

¹ <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5910a1.htm>

² Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

³ Reyes MP, Ostrea Jr. EM, Cabinian AE, et al (1989) Vancomycin during pregnancy: Does it cause hearing loss or nephrotoxicity in the infant? American Journal of Obstetrics and Gynecology. 161 (4) (pp 977-981).

exposed group that had abnormal conductive hearing at 3 months of age, which was not attributable to vancomycin and resolved by 12 months of age. No nephrotoxicity was noted.

Reviewer comment

Data from this study is included in the labeling of the RLD.

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 at the time of delivery.⁴ 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 neonate developed early-onset GBS sepsis or had a positive GBS antigen in their urine. No major adverse reactions were recorded either in the mothers or their newborns. None of the newborns had sensorineural hearing loss as assessed by brainstem auditory-evoked testing. Neonatal renal function was not examined, but all of the newborns were discharged in good condition.

(b) (4)

DPMH Literature Review

This reviewer did not identify any other published studies of vancomycin exposure during pregnancy.

Review of Pharmacovigilance Database

Twenty-five pregnancy cases have been reported to the applicant's pharmacovigilance database. Most of the cases involved serious life threatening infections, and all of the women (except for one) received vancomycin in addition to several other drugs. Only one case involved first trimester exposure. No adverse events or birth defects were reported in exposed neonates.

(b) (4)

Summary

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 studies on the safety of vancomycin exposure during the first trimester therefore it is not possible to draw any conclusions on the risk of birth defects following exposure to vancomycin in pregnancy. In addition, there are no data on the risk of miscarriage following fetal exposure to vancomycin. DPMH recommends the addition of data from the published studies to the Pregnancy subsection of labeling, under the Human Data heading.

⁴ Onwuchuruba CN, Towers CV, Howard BC, et al (2014) Transplacental passage of vancomycin from mother to neonate. American Journal of Obstetrics and Gynecology. 210 (4) (pp 352.e1- 352.e4).

Lactation

Nonclinical Experience

It is not known if vancomycin is present in animal milk. No additional nonclinical studies were submitted with this NDA.

Review of Human Lactation Data

Applicant's Literature Review

The applicant reviewed published data on vancomycin and breastfeeding. There is a single case report of a woman who received vancomycin 1 g intravenously every 12 hours from 35-38 weeks gestation.⁵ A single breastmilk sample was taken about 4 hours after the end of the infusion of the last maternal dose before delivery and was 12.7 mg/L.

Reviewer comment

Assuming the level reported is about the average colostrum level over the dosing interval, see below for the calculation of the estimated amount of vancomycin an infant would be exposed to in a day:

0.15 ml/kg/day (estimated milk consumption per day) X 12.7 mg/L=1.9 mg/kg/day.

This amount is 4.8% of the RLD's 40 mg/kg/day oral vancomycin dose for pediatrics. This level represents the level in colostrum milk, which is typically higher than mature milk.

(b) (4)

DPMH Literature Review

DPMH conducted a search of *Medications and Mother's Milk*⁶, the Drugs and Lactation Database (LactMed),⁷ and of published literature in PubMed and Embase using the search terms "vancomycin and lactation" and "vancomycin and breastfeeding."

In *Medications and Mother's Milk*, Thomas Hale, a breastfeeding expert, states the following regarding vancomycin and lactation:

"compatible with breastfeeding; its poor absorption from the infant's gastrointestinal tract would limit its systemic absorption."

Vancomycin is referenced in LactMed. The Summary of Use states:

⁵ Reyes MP, Ostrea Jr. EM, Cabinian AE, et al (1989) Vancomycin during pregnancy: Does it cause hearing loss or nephrotoxicity in the infant? *American Journal of Obstetrics and Gynecology*. 161 (4) (pp 977-981).

⁶ Hale, Thomas (2017) *Medications and Mothers' Milk*. Amarillo, Texas Hale Publishing.

⁷ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation for healthcare practitioners and women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

“Limited information indicates that vancomycin produces low levels in milk and because vancomycin is poorly absorbed orally, it is not likely to reach the bloodstream of the infant or cause any adverse effects in breastfed infants. No special precautions are required.”

Summary

Available limited data based on a single case report showed that vancomycin was present at a low level in milk. A single milk level is not sufficient to inform the levels of vancomycin in milk. (b) (4)

(b) (4). DPMH recommends that the single case report not be added to labeling (b) (4)

(b) (4) DPMH recommends that the following risk/benefit statement be included under the Risk Summary heading:

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

Infertility

Nonclinical Experience

Currently approved vancomycin labeling (the RLD) states that no fertility studies were conducted. No additional nonclinical studies were submitted with this NDA.

Applicant’s Literature Review

DPMH Literature Review

This reviewer did not identify any published studies on vancomycin and fertility effects.

Summary

Since there are no data that support an association between vancomycin and effects on fertility, Subsection 8.3, Females and Males of Reproductive Potential will not be added to vancomycin labeling.

CONCLUSION

The Pregnancy and Lactation subsections of vancomycin labeling were structured to be consistent with the PLLR. DPMH has the following recommendations for vancomycin labeling:

- **8.1 Pregnancy**
 - The “Pregnancy” subsection of vancomycin labeling was formatted in the PLLR format to include “Risk Summary” and “Data” sections.
- **8.2 Lactation**
 - The “Lactation” subsection of vancomycin labeling was formatted in the PLLR format to include the “Risk Summary” section.

DPMH LABELING RECOMMENDATIONS

DPMH discussed our labeling recommendations with DAIP. DPMH recommendations are below and reflect the discussions with DAIP. **See final labeling for all of the labeling revisions negotiated with the applicant.**

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on TRADENAME 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*). Vancomycin did not show adverse developmental effects when administered 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

A published study evaluated hearing loss and nephrotoxicity in infants of pregnant intravenous drug users treated with vancomycin for suspected or documented methicillin-resistant staphylococcal aureus in the second or third trimester. The comparison groups were 10 non-intravenous drug-dependent patients who received no treatment, and 10 untreated intravenous drug-dependent patients 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 culture and a high-risk penicillin allergy with resistance to clindamycin or unknown sensitivity who were administered vancomycin 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.

8.2 Lactation

Risk Summary

There are insufficient data to inform the levels of vancomycin in human milk. (b) (4)

There are no data on the effects 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.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEYLA SAHIN
04/19/2017

LYNNE P YAO
04/21/2017