

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211962Orig1s000

OTHER REVIEW(S)



Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Pregnancy and Lactation Labeling Review

Date: 2-11-2019 **Date Consulted:** 10-3-2018

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Division of Pediatric and Maternal Health

To: Division of Anti-Infective Products

Drug : Vancomycin hydrochloride for injection; NDA 211962

Proposed Indications: • Treatment of the following infections in adult and pediatric patients:

- Septicemia
- Infective Endocarditis
- Skin and Skin Structure Infections
- Bone Infections
- Lower Respiratory Tract Infections

Subject: Pregnancy Labeling of Excipient Nonclinical Safety Issue as Part of 505(b)(2) Application

Applicant: Xellia Pharmaceuticals, ApS

Materials Reviewed: • Applicant's proposed labeling

- Literature review
- Vancomycin hydrochloride for injection by Baxter NDA 050671 approved labeling (reference listed drug)

Consult Question: Please provide input on how to communicate the excipients' nonclinical reproductive safety findings in Pregnancy Labeling

INTRODUCTION

The applicant submitted a 505 (b) (2) NDA for Vancomycin hydrochloride for injection solution on May 23, 2018. The drug delivery system/formulation, "ready to use" (RTU) is different from the reference listed drug (RLD). This application was given Fast Track designation because it is considered advantageous to other vancomycin products as it does not require preparation (reconstitution and dilution), thawing, or refrigeration. This drug formulation includes two excipients the showed teratogenic effects in nonclinical reproductive studies. The Division of Anti-infective Products (DAIP) consulted the Division of Pediatric and Maternal Health (DPMH) on October 3, 2018, for assistance with communicating the pregnancy safety concern in labeling, based on the excipients' nonclinical findings. Of note, DPMH did a PLLR review for a different vancomycin 505(b)(2) application in 2017, which was approved in 2018¹; this PLLR version of vancomycin labeling was used as the model for labeling of the Pregnancy and Lactation sections of labeling for this application, based on DAIP's advice to the applicant. New expert reviews of the nonclinical reproductive and developmental toxicity data related to the excipients were submitted as a Major Amendment on 11-14-2018, and the goal date was extended 3 months.

BACKGROUND

Product Background

Vancomycin is a glycopeptide antibiotic that was first approved in 1964. The molecular weight is 1,485.71 Daltons. The half-life is 4 to 6 hours.

The proposed indications for this NDA, which are the same as the RLD's approved indications, are the following (in adults and pediatric patients):

- treatment of septicemia due to:
 - susceptible strains 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.
- treatment of endocarditis due to:
 - susceptible isolates of MRSA.
 - viridans group streptococci *Streptococcus gallolyticus* (previously known as *Streptococcus bovis*), *Enterococcus* species and *Corynebacterium* species. For

¹ See DPMH review for Vancomycin for injection NDA 209481 in DARRTS by Leyla Sahin, MD, dated 4-21-2017.

enterococcal endocarditis, use Vancomycin Injection 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.

- 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

- 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

- 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.

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

The RLD was approved in 1993. The currently approved labeling (9-28-2017) is not in the Physician Labeling Rule format. The Pregnancy section states that animal reproduction studies have not been conducted with vancomycin. 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 in labor 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.²

REVIEW

Pregnancy

Nonclinical Experience

Nonclinical studies with vancomycin were not conducted for this NDA. Nonclinical embryofetal studies were required for the two excipients, N-acetyl-D-alanine (NADA) and polyethylene glycol (PEG) 400. NADA is a novel excipient and PEG 400 levels are higher than other approved products (8.1 g vs 7.6 g for busulfan)³. The applicant conducted separate studies for each excipient. Reproduction studies in rabbits and rats using intravenous doses of NADA at approximately 6 and 7 times the maximum daily human dose (based on body surface area comparisons), resulted in fetal cardiovascular malformations in rabbits and no significant adverse embryofetal effects in rats. Increased delayed or incomplete ossifications of the metacarpals/metatarsals/phalanges were observed in both species, and increased ossification (fused jugal/maxilla bones) was observed in the high dose rabbit group. Maternal toxicity observed in rats at the highest dose tested was associated with increased incidence of litter loss. Animal reproduction studies conducted in rabbits administered intravenous PEG 400 during organogenesis at approximately 4.8 times the maximum daily human dose, based on body surface comparisons, resulted in fetal spinal malformations including scoliosis (thoracic and lumbar) and increased delayed or incomplete ossification of the cranial fontanelles, pubes, epiphyses and talus bones. No maternal toxicity was observed up to the maximum dose tested.

New expert reviews of the nonclinical reproductive and developmental toxicity data related to the excipients were submitted as a Major Amendment on 11-14-2018. FDA toxicologists concluded that the Major Amendment did not alter their assessment of the nonclinical study findings. Please refer to the toxicology review by Dr. Madisa Macon for further details.

Review of Human Pregnancy Data

Applicant's literature review

The applicant did not identify any published data on vancomycin use in pregnancy, other than what is included in the RLD labeling.

DPMH Literature Review

This reviewer did not identify any new published studies of vancomycin exposure during pregnancy since the literature review conducted in 4-2017 for Vancomycin for injection, NDA 209481.¹ Additionally, DPMH did not identify any published data on exposure to the excipients during pregnancy.

² <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5910a1.htm>

³ Based on communication with Dr. Madisa Macon, DAIP

Discussion and Conclusion

Nonclinical studies of the excipients showed the following teratogenic effects: spinal malformations in one species (rabbits) administered PEG 400 at 5 times the maximum daily human dose (based on body surface area (BSA)), and cardiovascular malformations in rabbits administered NADA at 6-7 times the maximum daily human dose (based on BSA). There are no human data on exposure to the excipients during pregnancy. There are no available data on first trimester use of vancomycin in pregnant women to assess the 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. Based on available nonclinical data, there is concern regarding the excipients' potential teratogenic effects if used in pregnancy. Therefore, it is appropriate to communicate this risk in the Risk Summary in the Pregnancy section, and in the Warnings and Precautions section of labeling. Because ossification in a developing fetus occurs beyond the first trimester, the risk messaging would not be limited to the first trimester.⁴ In developing the risk messaging, advice to use an excipient-free formulation of vancomycin in pregnancy is appropriate. In most situations, it is likely that an excipient-free formulation would be available. However, there may be situations where other formulations may not be available.

DPMH participated in labeling meetings with DAIP on 10-30-2018 and 11-1-2018 (included the Labeling Development Team (LDT)) where the approach to differentiating the potential risks due to the excipients was discussed. DAIP expressed the need for a boxed warning to differentiate this vancomycin formulation from other excipient-free vancomycins. DPMH felt that based on the W&P, CI, and Boxed Warning Guidance, the following situations are when a boxed Warning would be used:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug

OR

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)

OR

- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted.

Boxed warnings are most likely to be based on observed serious adverse reactions, but there are instances when a boxed warning based on an anticipated adverse reaction would be appropriate. For example, a contraindication to use during pregnancy based on evidence in humans or animals that drugs in a pharmacologic class pose a serious risk of developmental toxicity during pregnancy would usually be in a boxed warning for all drugs in that class, even those in which the adverse reaction has not been observed.

⁴ Filly R, Simpson G, Linkowski G. Fetal Spine morphology and maturation during the second trimester. J of Ultrasound Medicine 1987; 6:631-636.

The LDT recommended possibly including the risk information under the Limitations of Use section of labeling, and re-ordering the Warnings and Precautions subsections to place the Embryo-Fetal Toxicity Warning first.

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 did not review the published literature on vancomycin and breastfeeding.

DPMH Literature Review

This reviewer did not identify any new published studies of vancomycin and lactation since the literature review conducted in 4-2017 for Vancomycin for injection, NDA 209481.¹ Additionally, DPMH did not identify any published data on the excipients and lactation.

Summary

There are no data on the presence of vancomycin and the excipients NADA and PEG 400 in human or animal milk, the effects on the breastfed infant, or the effect on milk production.

Females and Males of Reproductive Potential

Infertility

Nonclinical Experience

Currently approved vancomycin labeling (the RLD) does not include any fertility information. No additional nonclinical studies were submitted with this NDA.

Applicant's Literature Review

The applicant did not review the published literature on vancomycin and infertility.

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.

DPMH LABELING RECOMMENDATIONS

DPMH recommendations are below. **See final labeling for all of the labeling revisions negotiated with the applicant.**

HIGHLIGHTS

- Embryo-Fetal Toxicity: May cause fetal harm. Use of this formulation in pregnancy is not recommended due to the excipients PEG 400 and N-acetyl-D-alanine (NADA). If vancomycin injection is needed during pregnancy, use a formulation free of PEG 400 and NADA (5.1, 8.1).

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

This formulation of vancomycin injection is not recommended for use during pregnancy because it contains the excipients PEG 400 and N-acetyl-D-alanine (NADA), which cause fetal malformations in animal reproduction studies. Rabbits administered intravenous doses of PEG 400 at approximately 5 times the maximum daily human dose (based on body surface area comparisons) during organogenesis resulted in fetal spinal malformations. Rabbits administered intravenous doses of NADA at approximately 6 and 7 times the maximum daily human dose (based on body surface area comparisons) during organogenesis resulted in fetal cardiovascular malformations. Advise pregnant women of the potential risk to the fetus. If vancomycin injection is needed during the first trimester of pregnancy, use a formulation free of PEG 400 and NADA. [See Use in Specific Populations (8.1)]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

This formulation of vancomycin injection is not recommended for use during pregnancy because it contains the excipients PEG 400 and N-acetyl-D-alanine (NADA), which cause fetal malformations in animal reproduction studies. If therapy with vancomycin is needed during the first trimester of pregnancy, use a formulation free of PEG 400 and NADA. 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 (based on body surface area comparisons), resulted in fetal cardiovascular malformations in rabbits and no significant adverse embryofetal effects in rats. 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*). 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. 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*). Advise pregnant women of the potential risk to the fetus.

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 controlled study evaluated hearing loss and nephrotoxicity in infants of 10 pregnant intravenous drug users treated with vancomycin (excluding the excipients PEG 400 and NADA) for suspected or documented methicillin-resistant staphylococcal aureus in the second or third trimester. The control groups were 10 uninfected non-intravenous drug-dependent patients who received no treatment and 10 uninfected untreated intravenous drug-dependent patients. 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 (excluding 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 4.8 times the maximum daily human dose, respectively, based on body surface comparisons) during organogenesis (gestation days 6 to 19) resulted in fetal spinal malformations including scoliosis (thoracic and lumbar) and increased delayed or incomplete ossification of the cranial fontanelles, 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 6-19) and pregnant rats (gestation days 6-17) 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 comparisons) resulted in heart ventricular septal defects and dilated aorta/aortic arch in rabbits, and no malformations in the rat. Increased delayed or incomplete ossifications of the metacarpals/metatarsals/phalanges were observed in both species, combined with increased ossification (fused jugal/maxilla bones) observed in high dose rabbit group. Maternal toxicity observed in rats at the highest dose tested was associated with increased incidence of litter loss.

No animal studies have been conducted to evaluate the potential reproductive and embryofetal effects of TRADENAME.

8.2 Lactation

Risk Summary

There are no data on the presence of vancomycin and the excipients NADA and PEG 400 in human or animal milk, the effects on the breastfed infant, or the effect on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

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/s/

LEYLA SAHIN
02/11/2019 04:21:22 PM

TAMARA N JOHNSON
02/11/2019 09:26:15 PM

LYNNE P YAO
02/12/2019 09:15:12 AM

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: October 31, 2018
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: NDA 211962
Product Name and Strength: Vancomycin Injection
500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL, and 2 g/400 mL
Applicant/Sponsor Name: Xellia Pharmaceuticals
FDA Received Date: September 24, 2018
OSE RCM #: 2018-1082-1
DMEPA Safety Evaluator: Deborah Myers, RPh, MBA
DMEPA Team Leader: Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

Division of Anti-Infective Products (DAIP) requested that we review the revised container label, overwrap labeling, and carton labeling for Vancomycin Injection (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that were made by the Office of Pharmaceutical Quality (OPQ) on September 19, 2018.^a

2 CONCLUSION

The revised container label, overwrap labeling, and carton labeling for Vancomycin Injection are acceptable from a medication error perspective. We have no further recommendations at this time.

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

^a Information request available at: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804b73cc>

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/s/

DEBORAH E MYERS
10/31/2018

OTTO L TOWNSEND
10/31/2018

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

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

Memorandum

Date: October 23, 2018

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

Eva Zuffova, Regulatory Project Manager, DAIP

Abimbola Adebawale, Associate Director for Labeling, 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 injection, for intravenous use

NDA: 211962

In response to DAIP's consult request dated July 11, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Vancomycin.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP on October 12, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAIP on October 18, 2018, 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.

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/s/

DAVID F FOSS
10/23/2018

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:	August 15, 2018
Requesting Office or Division:	The Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 211962
Product Name and Strength:	Vancomycin Injection; 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Xellia Pharmaceuticals
FDA Received Date:	May 23, 2018 and August 1, 2018
OSE RCM #:	2018-1082
DMEPA Safety Evaluator:	Sevan Kolejian, Pharm D, MBA
DMEPA Team Leader:	Otto L. Townsend, Pharm D

1 PURPOSE OF REVIEW VS REASON FOR REVIEW

As part of the approval process for Vancomycin Injection; 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL, the Division of Anti-Infective Products (DAIP) requested that we review the proposed packaging, label and labeling for areas that may lead to medication errors.

2 MATERIALS 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 (N/A)
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

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 FINDINGS AND RECOMMENDATIONS

Xellia Pharmaceuticals submitted a 505 (b)(2) New Drug Application for Vancomycin Injection, 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL, in ready to use plastic containers for intravenous use with the same active ingredients, indication, route of administration, dosage form and dosing regimen as the reference drug, Baxter's vancomycin injection, in galaxy plastic container, NDA N050671. However, the proposed product will have different product strengths (500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL, 2 g/400 mL vs. 500 mg/ 100 ml, 750 mg/150 ml, 1 g/200 ml) and the product storage conditions (applicant's product can be stored up to 25 °C while Baxter's product must be stored at or below -20°C (-4°F).

4 CONCLUSION

Our evaluation of the proposed packaging, label and labeling did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Vancomycin injection that Xellia Pharmaceuticals submitted on August 1, 2018, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Vancomycin Injection		
Product Name	Vancomycin Hydrochloride in plastic container	Vancomycin injection
Initial Approval Date	NDA 050671 4/29/1993	N/A
Active Ingredient	Vancomycin	Vancomycin
Indication	Vancomycin is indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (beta-lactam-resistant) staphylococci. It is indicated for penicillin-allergic patients, for patients who cannot receive or who have failed to respond to other drugs, including the penicillins or cephalosporins, and for infections caused by vancomycin-susceptible organisms that are resistant to other antimicrobial drugs. Vancomycin is indicated for initial therapy when methicillin-resistant staphylococci are suspected, but after	(b) (4)

susceptibility data are available, therapy should be adjusted accordingly.

Vancomycin is effective in the treatment of staphylococcal endocarditis. Its effectiveness has been documented in other infections due to staphylococci, including septicemia, bone infections, lower respiratory tract infections, skin and skin structure infections.

When staphylococcal infections are localized and purulent, antibiotics are used as adjuncts to appropriate surgical measures.

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

Vancomycin has been reported to be effective for the treatment of diphtheroid endocarditis.

Vancomycin has been

	<p>used successfully in combination with either rifampin, an aminoglycoside, or both in early-onset prosthetic valve endocarditis caused by <i>S. epidermidis</i> or diphtheroids. Specimens for bacteriologic cultures should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to vancomycin.</p> <p>To reduce the development of drug-resistant bacteria and maintain the effectiveness of vancomycin and other antibacterial drugs, vancomycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.</p>	<p style="text-align: right;">(b) (4)</p> <p>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. 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.</p>
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Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength	500 mg/ 100 ml, 750 mg/150 ml, 1 g/200 ml	500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL, 2 g/400 mL
Dose and Frequency	<p>Adult Population: The usual daily intravenous dose is 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours. Each dose should be administered at no more than 10 mg/min or over a period of at least 60 minutes, whichever is longer. Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose.</p> <p>Pediatric Patients: The usual intravenous dosage of vancomycin is 10mg/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.</p> <p>Neonates: In pediatric patients up to the age of 1 month, the total daily intravenous dosage may be lower. In neonates, an</p>	<p>Adults</p> <p>The usual daily intravenous dose is 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours. Each dose (b) (4) over a period of (b) (4) 60 minutes, (b) (4) Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose.</p> <p>Pediatric patients</p> <p>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.</p> <p>(b) (4)</p>

	<p>initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the 1st week of life and every 8 hours thereafter up to the age of 1 month. Each dose should be administered over 60 minutes. In premature infants, vancomycin clearance decreases as postconceptional age decreases. Therefore, longer dosing intervals may be necessary in premature infants. Close monitoring of serum concentrations of vancomycin is recommended in these patients.</p>											
How Supplied	<p>Vancomycin Injection, USP is supplied as a frozen, iso-osmotic, premixed solution in either 5% Dextrose or 0.9% Sodium Chloride in a 100 mL, 150 mL, 200 mL single dose GALAXY plastic container (PL 2040) in the following vancomycin (b) (4) dose.</p>	<p>Vancomycin Injection ((b) (4)) is supplied as ready-to-use (b) (4) single-dose (b) (4) :</p> <table border="1"> <thead> <tr> <th>NDC number</th> <th>Packaging configuration</th> </tr> </thead> <tbody> <tr> <td>70594-041-02</td> <td>6 x 500 mg/100 mL</td> </tr> <tr> <td>70594-041-03</td> <td>12 x 500 mg/100 mL</td> </tr> <tr> <td>70594-042-02</td> <td>6 x 1 g/200 mL</td> </tr> <tr> <td>70594-042-03</td> <td>12 x 1 g/200 mL</td> </tr> </tbody> </table>	NDC number	Packaging configuration	70594-041-02	6 x 500 mg/100 mL	70594-041-03	12 x 500 mg/100 mL	70594-042-02	6 x 1 g/200 mL	70594-042-03	12 x 1 g/200 mL
NDC number	Packaging configuration											
70594-041-02	6 x 500 mg/100 mL											
70594-041-03	12 x 500 mg/100 mL											
70594-042-02	6 x 1 g/200 mL											
70594-042-03	12 x 1 g/200 mL											
Storage	<p>Store at or below -20°C (-4°F).</p>	<p>Store below 25°C (77°F), in original package. Product should be used within 28 days of removal from aluminum overpouch.</p>										
Container Closure	<p>Baxter’s Galaxy Plastic container</p>	<p>Transparent Plastic container</p>										

APPENDIX F. LABELS AND LABELING

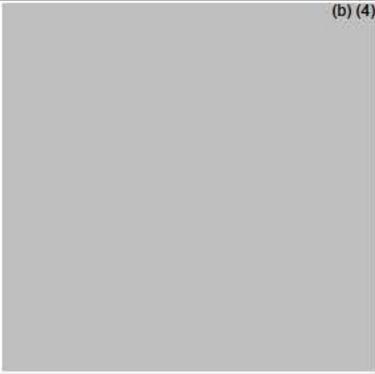
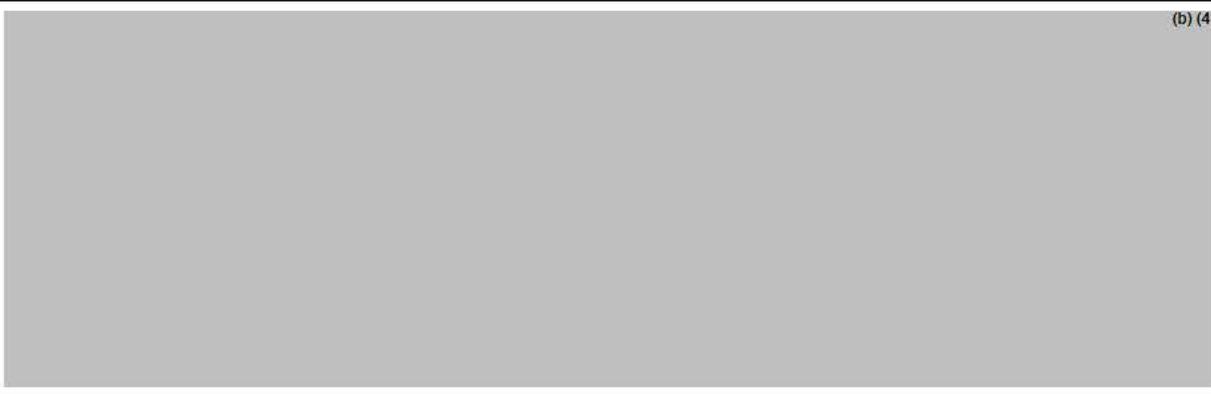
F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Vancomycin injection labels and labeling submitted by Xellia Pharmaceuticals on August 1, 2018.

- Container labels received on August 1, 2018
- Overwrap labeling received on August 1, 2018
- Carton labeling received on August 1, 2018
- Prescribing Information (Image not shown) received on August 1, 2018, available in EDR <\\cdsesub1\evsprod\nda211962\0005\m1\us\draft-package-insert-clean-0005-word.docx>

F.2 Label and Labeling Images

1. Vancomycin Injection 500 mg/100 mL

Container label	Overwrap labeling
 (b) (4)	 (b) (4)
Carton Labeling	
 (b) (4)	

^a 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SEVAN H KOLEJIAN
08/15/2018

OTTO L TOWNSEND
08/16/2018