CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213895Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	August 18, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 213895
Product Name and Strength:	Vancomycin Injection, 5 grams/100 mL (50 mg/mL
Applicant/Sponsor Name:	Xellia Pharmaceuticals ApS (Xellia)
OSE RCM #:	2021-461-4
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted their revised container label and carton labeling received on August 18, 2021 for Vancomycin. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Vancomycin (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 Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Myers, D. Label and Labeling Review Memo for Vancomycin (NDA 213895). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 AUG 16. RCM No.: 2021-461-3.

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/s/

DEBORAH E MYERS
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VALERIE S VAUGHAN
08/18/2021 02:50:48 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	August 16, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 213895
Product Name and Strength:	Vancomycin Injection, 5 grams/100 mL (50 mg/mL)
Applicant/Sponsor Name:	Xellia Pharmaceuticals ApS (Xellia)
OSE RCM #:	2021-461-3
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on August 16, 2021 for Vancomycin. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Vancomycin (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to an information request (IR) from DAI.[a]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. As currently presented the Box Warning is included on the side panel of the container label and carton labeling. A Box Warning is considered to be "critical information" that should be prominently displayed on the principal display panel (PDP) of the container label and carton labeling.[b] Therefore, to minimize the risk of the Box Warning being overlooked and to increase its prominence we have provided our recommendation in *Section 3* below that the

[a] Smith, C. FDA Communication: NDA 213895 DMEPA Boxed Warning IR for Vancomycin Injection (NDA 213895). Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2021 AUG 10. NDA 213895. Available from: \\CDSESUB1\evsprod\nda213895\0024\m1\us\12-cover\cover-0024-att2-ir.pdf.
[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 134-151). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

Applicant relocate the current Box Warning from the side panel to the PDP of the container label and carton labeling.

3 RECOMMENDATIONS FOR XELLIA PHARMACEUTICALS APS

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

As currently presented the Box Warning is included on the side panel of the container label and carton labeling. A Box Warning is considered to be "critical information" that should be prominently displayed on the principal display panel (PDP) of the container label and carton labeling.[c] Therefore, to minimize the risk of the Box Warning being overlooked and to increase its prominence we recommend that you relocate the current Box Warning from the side panel to the PDP of the container label and carton labeling. To ensure sufficient space on the PDP of the container label, you may consider relocating the "Each bottle contains 5 g of vancomycin" statement from its current location on the PDP to the side panel, as well as adjusting the font size of the established name and strength statement.

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[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 134-151). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

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DEBORAH E MYERS
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VALERIE S VAUGHAN
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	August 6, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 213895
Product Name and Strength:	Vancomycin Injection, 5 grams/100 mL (50 mg/mL)
Applicant/Sponsor Name:	Xellia Pharmaceuticals ApS (Xellia)
OSE RCM #:	2021-461-2
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

This memorandum captures our assessment of proposed revised language for the box warning in the prescribing information, container label, and carton labeling for this application.

2 DISCUSSION AND CONCLUSION

The Division of Anti-Infectives (DAI) communicated our previous container label and carton labeling recommendation for the box warning statement to revise the box warning to state:

> *"Warning: Not recommended for use during the first or second trimester of pregnancy (see Prescribing Information)."*

Subsequently, the Applicant requested clarification on whether there would be a difference in the box warning language included in the prescribing information, which states:

> (b) (4)
>
> 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 excipient polyethylene glycol (PEG 400), which resulted in fetal malformations in animal reproduction studies. (5.1, 8.1)

During an internal labeling meeting held on August 6, 2021, the Division of Anti-Infectives (DAI) and the Division of Pediatrics and Maternal Health (DPMH) determined that the box warning title, "WARNING: [redacted] (b) (4) would be revised to "WARNING: POTENTIAL RISK OF EXPOSURE TO EXCIPTIENT DURING THE FIRST OR SECOND TRIMESTER OF PREGNANCY." The revised title provides additional context to the specific trimesters for which use of a different formulation of Vancomycin injection is advised due to the potential risk to the fetus posed by potential exposure to the polyethylene glycol (PEG 400) excipient contained in this product. Additionally, DPMH voiced concern that the recommended language for the box warning on the container label and carton labeling does not match the language used in the box warning in the PI. We note that our previous recommendation for the box warning on the container label and carton labeling was intended to provide a concise but informative warning to aid healthcare providers in their use of this product given the potential risk to the fetus if used during the first or second trimester of pregnancy. Additionally, we note that the box warning references subsection 8.1 (Pregnancy) of the full prescribing information, which states:

> *This formulation of Vancomycin Injection administered intravenously or orally is not recommended for use during the first or second trimester of pregnancy because it contains the excipient, PEG 400, which caused fetal malformations in animal reproduction studies following intravenous administration (see Data). Advise pregnant women of the potential risk to the fetus. If therapy with Vancomycin Injection is needed during the first or second trimester of pregnancy, use other available formulations of vancomycin free of PEG 400.*

During the internal meeting DAI and DPMH reached concurrence that the language used in the box warning on the container label and carton labeling should be revised to match the title of the box warning in the PI based on the *unknown* potential for the fetus to be exposed to PEG 400 during the first and second trimester of pregnancy. Thus, DAI and DPMH recommends the box warning language on the container label and carton labeling be revised to:

Warning: Potential risk of exposure to excipient during the first or second trimester of pregnancy (see Prescribing Information)

Based on the discussion, we do not object to the revised language for the box warning located on the container label and carton labeling.

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DEBORAH E MYERS
08/06/2021 05:55:02 PM

VALERIE S VAUGHAN
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	August 4, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 213895
Product Name and Strength:	Vancomycin Injection, 5 grams/100 mL (50 mg/mL)
Applicant/Sponsor Name:	Xellia Pharmaceuticals ApS (Xellia)
OSE RCM #:	2021-461-1
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

This memorandum is to amend our previous container label and carton labeling recommendation that we made during the initial phase of review for this application. [a]

2 DISCUSSION AND RECOMMENDATION

During an internal labeling meeting held on August 3, 2021, the Division of Anti-Infectives (DAI) reached concurrence with the Division of Pediatrics and Maternal Health (DPMH) regarding the language to include in the Box Warning to inform healthcare providers about the use of this product in pregnant women. Specifically, it was determined that this product should not be used in pregnant women during the first or second trimester. Thus, in an effort to minimize the risk for medication errors, we are amending our previous recommendation to align with the Box Warning recommendation included in the proposed PI.

Table 1 below includes the identified medication error issue with the proposed container label and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

[a] Myers, D. Label and Labeling Review Memo for Vancomycin (NDA 213895). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 JUL 28. RCM No.: 2021-461.

Table 1. Identified Issues and Recommendations for Xellia Pharmaceuticals ApS (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	We note that this product should not be administered during the first or second trimester of pregnancy due to fetal malformation in animal reproduction studies associated with polyethylene glycol (PEG 400).	This important safety information should be included on the container label and carton labeling to alert users that the product should not be used to prepare vancomycin doses that will be administered to pregnant women during the first or second trimester.	To alert healthcare providers to not use this product in pregnant women during the first or second trimester we recommend that you add the Box Warning statement "Warning: Not recommended for use during the first or second trimester of pregnancy (see Prescribing Information)" to your proposed container label and carton labeling. For example: Warning: Not recommended for use during the first or second trimester of pregnancy (see Prescribing Information)

3 CONCLUSION

To align the language in DAI's Box Warning recommendation for the proposed PI with the proposed container label and carton labeling, we have provided our recommendation in Table 1 for the Applicant. We ask that the Division convey Table 1 in its entirety to Xellia Pharmaceuticals ApS so that the recommendation is implemented prior to approval of this NDA.

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DEBORAH E MYERS
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VALERIE S VAUGHAN
08/04/2021 10:34:12 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
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

Division of Pediatric and Maternal Health Review

Date: 8/4/2021 **Date consulted:** 6/22/2021

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

To: Division of Anti-Infectives (DAI)

Drug: Vancomycin Injection 500 mg/10 mL, 1 g/20 mL and 5 g/100 mL (50 mg/mL) liquid formulation in vials, for intravenous use or for oral use

NDA: 213895

Applicant: Xellia Pharmaceticals USA, LLC

Subject: New NDA, Labeling Review related to pregnancy and lactation

Proposed Indication: a glycopeptide antibacterial indicated in adult and pediatric patients:
Vancomycin Injection administered intravenously is indicated for the treatment of:

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

Vancomycin Injection administered orally is indicated for the treatment of:

- Clostridioides difficile associated diarrhea
- Enterocolitis caused by Staphylococcus aureus (including methicillin-resistant strains)

Materials
Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 213895
- DAI consult form for DPMH, DARRTS Reference ID 4815923
- Prior DPMH PLLR Review for Vancomycin Injection NDA 211962, entitled "Pregnancy Labeling of Excipients (NADA and PEG-400)," by Kristie Baisden, DO, dated April 20, 2021, DARRTS Reference ID: 4782308.
- Prior DPMH PLLR Review for Vancomycin Capsules NDA 050606, by Leyla Sahin, MD, dated December 4, 2019, DARRTS Reference ID: 4528986.
- Prior DPMH PLLR Review for Vancomycin Injection NDA 211962, entitled "Pregnancy Labeling of Excipient Nonclinical Safety Issue as Part of 505(b)(2) Application," by Leyla Sahin, MD, dated February 11, 2019, DARRTS Reference ID: 4389256.
- Prior DPMH PLLR Review for Vancomycin Injection NDA 209481, by Leyla Sahin, MD, dated April 4, 2017, DARRTS Reference ID: 4086133.

Consult Question:

"Based on the previously submitted nonclinical and clinical PK data, DAI is interested in any comments/recommendations you may have regarding Section 8 of this vancomycin PI, the language under the Boxed Warning and Warning regarding the risk of embryo-fetal toxicity."

INTRODUCTION AND BACKGROUND

On February 26, 2021, the applicant (Xellia Pharmaceuticals USA, LLC) submitted a new original NDA 213895 for vancomycin injection for approval. The Division of Anti-Infections (DAI) consulted the Division of Pediatric and Maternal Health (DPMH) on June 22, 2021, to assist with the Warnings and Precaution and Pregnancy and Lactation subsections of labeling.

Regulatory History

- Vancomycin is a glycopeptide antibiotic that was first approved in 1964.
- On September 20, 2019, the applicant submitted vancomycin injection, NDA 213895, in adult and pediatric patients for intravenous treatment of:
    - Septicemia
    - Infective Endocarditis
    - Skin and Skin Structure Infections
    - Bone Infections
    - Lower Respiratory Tract Infections

  For Oral treatment of:
    - Clostridioides difficile-associated diarrhea
    - Enterocolitis caused by Staphylococcus aureus (including methicillin-resistant strains)

  This was submitted under section 505(b)(2) pathway of the Federal Food, Drug and Cosmetic Act. The listed drug (LD) is Vancocin® Hydrochloride (Vancomycin Hydrochloride for Injection, USP) approved under ANDA 060180 (currently discontinued) and ANDA 062663, the current Reference Standard (RS) for the in vitro bridging.

- The proposed formulation is considered advantageous to other vancomycin products for intravenous administration currently available on the U.S. market as it is ready for us and reconstitution or thawing is not required.
- On March 20, 2020, FDA responded in a Complete Response due to concerns related to product quality and requesting additional nonclinical toxicology assessment for any leachable that exceeds 5 mcg/day.
- On February 26, 2021, the applicant responded to the Complete Response and included additional information and minor changes within the submission, including additional data to support the proposed prescribing information related to perceived risk of use during pregnancy

(b) (4)

- On June 22, 2021, DAI consulted DPMH to assist with the Warnings and Precautions and Section 8 of the labeling. DAI notes that "given the potential risk of embryo-fetal toxicity based on the findings in the nonclinical studies, the labeling for this vancomycin product would include a Boxed Warning and a Warning regarding the risk of embryo-fetal toxicity."

Drug Characteristics

The proposed formulation differs from the LD in terms of the inactive ingredients. More specifically, besides sodium hydroxide, as a pH adjusting agent, the applicant's product contains L-Lysine Hydrochloride and NADA, as stabilizers, and PEG 400 and water for injection as solvents. NADA is a non-compendial excipient, not listed in the FDA Inactive Ingredient Database.

The proposed formulation was developed following approval of Vancomycin Injection, USP, NDA 211962, ready to use (RTU) premixed solution, which was approved in February 2019. Both products are similar in composition and are both ready for use. In contrast to NDA 211962, current proposed formulation has a lower concentrations of the inactive ingredients NADA and PEG 400 per gram of vancomycin with RTU: vial ratio of 3 for NADA and 1.8 for PEG 400. The proposed formulation can be administered intravenously and orally.

REVIEW

PREGANACY

Previous DPMH reviews[1, 2, 3, 4] have concluded that the "there are no available data on first trimester use of [oral or intravenous administered] 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." An updated literature search was performed on Embase and Pubmed, and there are no new relevant articles identified on vancomycin use during pregnancy. Vancomycin is used in the third trimester of pregnancy as noted in previous DPMH reviews of vancomycin. The Center for Disease Control (CDC) guidelines on the prevention of perinatal group B streptococcus (GBS) recommend the use of intravenous vancomycin for intrapartum prophylaxis of GBS in penicillin-allergic pregnant people at high risk for anaphylaxis if their isolate is resistant to clindamycin (or if the susceptibility is unknown).[5] DPMH agrees with the previous conclusions on the effect of vancomycin on pregnancy outcomes.

The proposed formulation of vancomycin injection contains two additional excipients NADA and PEG 400 which have been found to cause fetal malformations in animal reproduction studies. Reproduction studies in rabbits and rats using intravenous doses of NADA at approximately 96 and 58 times the MRHD, respectively, based on systemic exposures of NADA resulted in maternal toxicity and fetal spinal and cardiovascular malformations in rabbits, and maternal toxicity with no adverse embryo-fetal effects in rats. The observed-adverse-effect-level (NOAEL) of NADA in embryo-fetal studies (EFD) in rats and rabbits are 26.3 and 31.6 times higher than the MRHD, respectively. Although the oral bioavailability of NADA is unknown, based on animal studies, there is no concern for human embryofetal toxicity with NADA exposure during pregnancy from either route of administration. In EFD studies with PEG 400 intravenously administered in rabbits at approximately 13 times the MRHD based on systemic exposures of PEG 400, during organogenesis, resulted in fetal spinal malformations. However, the exposure margin to the no-NOAEL is only 2.3-fold higher than the MRHD based on PK comparisons of PEG 400. This is confirmed in discussion with DAI Pharmacology Toxicology team.

Because the NOAEL for intravenously administered PEG 400 in EFD studies in rabbits is only about 2.3-fold higher than the MRHD and there are other vancomycin injections available on the market without these two excipients, DPMH agrees with DAI in the need to develop language to communicate such a risk in the labeling by including a Boxed Warning and a Warnings and Precautions statement. Because ossification in a developing fetus occurs beyond the first

[1] Prior DPMH PLLR Review for Vancomycin Injection NDA 211962, entitled "Pregnancy Labeling of Excipients (NADA and PEG-400)," by Kristie Baisden, DO, dated April 20, 2021, DARRTS Reference ID: 4782308.
[2] Prior DPMH PLLR Review for Vancomycin Capsules NDA 050606, by Leyla Sahin, MD, dated December 4, 2019, DARRTS Reference ID: 4528986.
[3] Prior DPMH PLLR Review for Vancomycin Injection NDA 211962, entitled "Pregnancy Labeling of Excipient Nonclinical Safety Issue as Part of 505(b)(2) Application," by Leyla Sahin, MD, dated February 11, 2019, DARRTS Reference ID: 4389256.
[4] Prior DPMH PLLR Review for Vancomycin Injection NDA 209481, by Leyla Sahin, MD, dated April 4, 2017, DARRTS Reference ID: 4086133.
[5] https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5910a1.htm Accessed 7/8/2021.

trimester, the risk messaging would not be limited to the first trimester.[6] In developing the risk messaging, advice to use an excipient-free formulation of vancomycin for intravenous administration in pregnancy is appropriate.

In discussion with DAI Clinical Pharmacology and Pharmacology Toxicology teams, it was noted that the quality of the articles submitted by the applicant was not adequate for determining a PEG 400 oral % bioavailability value. Therefore, it is possible that oral administration may result in sufficient systemic absorption to result in potential harm to the pregnant fetus. DPMH recommends to also include oral administration under Warnings and Precautions and the Boxed Warning.

Due to the presence of the Boxed Warning, a concern for adverse embryofetal effect, and that there are other vancomycin formulations without PEG 400 and NADA on the market, conducting a postmarketing pregnancy safety study is not feasible. Therefore, DPMH does not recommend a postmarketing pregnancy study at this time.

LACTATION

Previous DPMH reviews[2,3,4] concluded that there are insufficient data to inform the levels of vancomycin in human milk and there are no data on the effects of vancomycin on the breastfed infant or milk production. DPMH has reviewed a case report of a single colostral milk sample taken 4 hours after an intravenous dose of vancomycin administered at delivery. This patient has also received vancomycin 1 g intravenously every 12 hours from 35 to 38 weeks gestation.[7] Because available limited data based on a single case report showed that vancomycin was present at a low level in milk and a single milk level is not sufficient to inform the levels of vancomycin in milk, DPMH has previously recommended that the single case report not be added to labeling. Because vancomycin is not absorbed well systematically by oral administration, there was minimal concerns over significant absorption of vancomycin through breastmilk. DPMH recommended that information regarding poor oral absorption be added to the labeling. This reviewer agrees. An updated literature search was performed, and no additional articles were found on the use of vancomycin during lactation. Additionally, there are no articles on the presence of NADA and PEG 400 in milk, the effects on the breastfed infant, or the effect on milk production. It is not known if vancomycin, NADA or PEG 400 is present in animal milk. No animal study regarding lactation was submitted with this NDA.

Because the current vancomycin formulation is not significantly different from the previous formulation submitted under NDA 211962, no postmarketing lactation study was issued at approval of NDA 211962, and no new postmarketing safety issue was identified, DPMH does not recommend a postmarketing lactation study at this time.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Previous DPMH reviews of vancomycin did not identify any published literature regarding vancomycin and fertility. No additional relevant article was identified in an updated literature

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

[7] Reyes MP, Ostrea Jr. EM, Cabinian AE et al. Vancomycin during pregnancy: does it cause hearing loss or nephrotoxicity in the infant? Am J Obstet Gynecol. 1989; 161:977-81.

search. Long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of vancomycin was found in standard laboratory tests. No definitive fertility studies have been performed in animals or humans.

Because of the potential embryofetal toxicity related to the excipients of this product and a Boxed Warning exists for this product, therefore, DPMH recommends Pregnancy Testing under subsections 2.1, 8.3 and section 17.

LABELING RECOMMENDATIONS

DPMH proposes edits to subsections 2.1, 5.1, 8.1, 8.2, 8.3, and section 17 of labeling for the new NDA and in compliance with the PLLR (see below), which reflect input from the DAI Clinical, Clinical Pharmacology, and Pharmacology Toxicology Teams. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

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/s/

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08/04/2021 09:40:06 AM

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

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

Memorandum

Date: August 2, 2021

To: Alma Davidson, M.D.
Division of Anti-Infectives (DAI)

Christopher Smith, Regulatory Project Manager, DAI

Abimbola Adebowale, Associate Director for Labeling, DAI

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 or oral use

NDA: 213895

In response to DAI's consult request dated July 17, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Vancomycin.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAI on July 21, 2021, 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 July 23, 2021, 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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DAVID F FOSS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	July 28, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 213895
Product Name and Strength:	Vancomycin Injection, 5 grams/100 mL (50 mg/mL)
Applicant/Sponsor Name:	Xellia Pharmaceuticals ApS (Xellia)
OSE RCM #:	2021-461
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted their revised container label and carton labeling received on July 23, 2021 for Vancomycin Injection.[a] The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Vancomycin Injection (Appendix A) to determine if they are acceptable from a medication error perspective. The container label and carton labeling revisions are in response to an information request dated July 17, 2021 combining our previous DMEPA container label and carton labeling recommendations,[b] as well as container label and carton labeling recommendations from the Office of Pharmaceutical Quality (OPQ).[c]

[a] Cover Letter: Amendment – Response to Information Request (Container Label) for Vancomycin Injection (NDA 213895). Copenhagen S (Denmark): Xellia Pharmaceuticals ApS; 2021 JULY 23. Available from: \\CDSESUB1\evsprod\nda213895\0023\m1\us\12-cover\cover-0023-lab-ame.pdf.
[b] Myers D. Label and Labeling Review for Vancomycin Injection (NDA 213895). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 29. RCM No.: 2019-1951.
[c] Smith, C. FDA Communication: NDA 213895 Proposed Labeling Revisions Information Request (IR) for Vancomycin Injection. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2021 JUL 17. NDA 213895. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806034fd&_afrRedirect=240024948345 8502.

2 BACKGROUND/REGULATORY HISTORY

On February 26, 2021, Xellia submitted their Class 2 Resubmission[d,e] for Vancomycin Injection (NDA 213895) to provide their responses to the product quality and nonclinical toxicology deficiencies, as well as additional information and minor changes, included in the Agency's Complete Response Letter (CRL), dated March 20, 2020.[f] This resubmission included revised draft prescribing information. However, as our previous container label and carton labeling recommendations[g] were not included in the March 20, 2020 CRL, there was no revised container label and carton labeling included in the resubmission.

On March 26, 2021, the Agency provided Xellia confirmation that the Agency considers their February 26, 2021, resubmission a complete class 2 response to the Agency's CRL dated March 20, 2020.[h]

On July 17, 2021, DAI sent an information request combining our previous DMEPA container label and carton labeling recommendations, as well as container label and carton labeling recommendations from the Office of Pharmaceutical Quality (OPQ). Subsequently, on July 23, 2021, Xellia submitted their revised container label and carton labeling for Vancomycin Injection.

3 FINDINGS AND RECOMMENDATIONS

Prior to the issuance of the CRL, we evaluated the prescribing information (PI), as well as the container label and carton labeling for Vancomycin Injection and provided recommendations to address medication error concerns. We note that Xellia confirmed in their July 23, 2021 submission of their revised container label and carton labeling that their intended format of the expiration date will include only numerical characters expressed as "Exp MM YYYY." Additionally, we note that Xellia's resubmission includes a revised proposed PI (see Appendix A). Table 1 includes the identified medication error issues with the proposed PI, as well as

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[d] Cover Letter: Resubmission – Response to Complete Response (Product Quality and Nonclinical Toxicology) for Vancomycin Injection (NDA 213895). Copenhagen S (Denmark): Xellia Pharmaceuticals ApS; 2021 FEB 26. Available from: \\CDSESUB1\evsprod\nda213895\0018\m1\us\12-cover\cover-0018-resub.pdf.

[e] Attachment to Response to Complete Response Letter – Additional Data to support proposed prescribing information related to perceived risk of use during pregnancy for Vancomycin Injection (NDA 213895). Copenhagen S (Denmark): Xellia Pharmaceuticals ApS; 2021 FEB 26. Available from: \\CDSESUB1\evsprod\nda213895\0018\m1\us\12-cover\cover-0018-att2-add.pdf.

[f] Smith, C. FDA Communication: Complete Response Letter for Vancomycin Injection. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2020 MAR 20. NDA 213895. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8054d43b&_afrRedirect=587195366771698.

[g] Myers D. Label and Labeling Review for Vancomycin Injection (NDA 213895). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 29. RCM No.: 2019-1951.

[h] Smith, C. FDA Communication: Acknowledge – Class 2 Resubmission for Vancomycin Injection. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2021 MAR 26. NDA 213895. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805e0e0b&_afrRedirect=587271874999981.

grammatical issues, our rationale for concern, and the proposed recommendation to minimize the risk for medication error or provide clarity.

Table 1. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	As currently presented, the strength is stated as "5 g/100 mL" throughout the prescribing information (PI), which does not include the quantity per milliliter statement, "50 mg/mL" that is currently included in Section 2, *Dosage and Administration, Preparation and Stability.*	Inconsistent product strength statements could lead to confusion, as well as wrong strength or wrong dose medication errors. Product strength statements should be consistent throughout all elements of the labeling (e.g., container, carton, and prescribing information).[i]	For consistency and to decrease the potential for wrong strength or wrong dose medication errors, we recommend the consistent use of the strength statement, "5 g/100 mL (50 mg/mL)," where applicable throughout the PI (e.g., Highlights of Prescribing Information, Section 3, *Dosage Forms and Strengths*, Section 11, *Description*, and Section 16, *How Supplied/Storage and Handling)*. For example, revise the current statements, "5 g/100 mL" to instead "5 g/100 mL (50 mg/mL)."
Highlights of Prescribing Information			
1.	As currently presented, under the header; *Dosage and Administration*, *For intravenous use, Adult Patients*, the unit of measure is abbreviated as, "g" and not written	Abbreviations should be written out (defined), followed by the abbreviation itself enclosed by parentheses, with their first appearance in the document. Subsequent references to the	Following the Arabic numeral "2" replace the current "g" with "grams (g)" and following "0.5" replace the current "grams (g)" with "g." For example, "2 grams (g) divided either as 0.5 g every..."

[i] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 380 - 381). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

Table 1. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	out (defined) as "grams" after the first mention of the abbreviation (i.e., "2 g divided either as 0.5 grams (g) every…").	abbreviation can be made just by the abbreviation letter(s) alone.	Alternatively, spell out the unit of measure (i.e., grams) throughout the document.
2.	As currently presented, under the header; *Dosage and Administration*, *For intravenous use,* the subheadings "Adult Patients" and "Pediatric Patients" are underlined, (b) (4)	Inconsistent labeling format may contribute to confusion that can result in medication error.	To provide consistency and clarity, underline the subheading (b) (4) (b) (4)
3.	As currently presented, under the header; *Dosage and Administration*, *For oral use*, both *Adult Patients* and *Pediatric Patients*, states the treatment duration as "7 to 10 days."	The shorter duration (7) in the range could be missed or misinterpreted because it is not followed by the appropriate unit of time (days).	To provide clarity and minimize the risk for misinterpretation, add the unit of time, "days" after the Arabic numeral "7." For example, "7 days to 10 days."
Full Prescribing Information – Section 2.2 *Dosage and Administration, Oral Administration*			
1.	As currently presented, the treatment duration reads "…for 7 to 10 days."	The shorter duration (7) in the range could be missed or misinterpreted because it is not followed by the appropriate unit of time (days).	To provide clarity and minimize the risk for misinterpretation, add the unit of time, "days" after the Arabic numeral "7." For example, "…for 7 days to 10 days."
Full Prescribing Information – Section 3 *Dosage Forms and Strengths*			
1.	As currently presented, the appropriate	A description of identifying characteristics is required by	We recommend that the description of identifying

Table 1. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	information to facilitate identification of the dosage form is not included.	21 CFR 201.57(c)(4)(ii) and can be used to help mitigate the risk of administering deteriorated or contaminated drug for this parenteral dosage form.	characteristics of the dosage form, such as color (e.g., colorless to light yellow or light brown) and clarity (e.g., clear solution) and any other identifying characteristics, be added in accordance with 21 CFR 201.57(c)(4)(ii) (i.e., as stated in Section 16.1, *How Supplied*, "clear, colorless to light yellow or light brown solution").
Full Prescribing Information – Section 16 *How Supplied/Storage and Handling*			
1.	Under the subheading, 16.1, *How Supplied*, there is no space included between the Arabic numeral and the unit of measurement (i.e. "5g").	Presenting a dose, strength, or volume without a space between the numeral and unit of measurement can negatively impact readability.	To improve readability, add a space between the Arabic numeral "5" and the unit of measurement "g." For example, "…5 g/100 mL,…"
Container Label and Carton Labeling			
1.	We note that the Prescribing Information indicates that this product should not be administered to pregnant women due to embryofetal toxicity associated with polyethylene glycol (PEG 400) and N-acetyl D-alanine (NADA) excipients.	This important safety information should be included on the container label and carton labeling to alert users that the product should not be used to prepare vancomycin doses that will be administered to pregnant women.	If the Division of Anti-Infectives (DAI) determines that this product should not be used to prepare vancomycin doses for pregnant women due to the embryofetal toxicity, we recommend the container label and carton labeling include a warning statement accompanied by a graphic symbol to alert healthcare providers to not use this product in pregnant women. For example:

Table 1. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			Not for pregnant women 

4 CONCLUSION

The proposed prescribing information (PI), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 3 for the Division.

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Prescribing Information (PI)

- Clean proposed (Draft) PI received on February 26, 2021, available at the following link: \\CDSESUB1\evsprod\nda213895\0018\m1\us\word\draft-lab-text-lab-text-cl-w.docx.
- Track changes PI received on February 26, 2021, available at the following link: \\CDSESUB1\evsprod\nda213895\0018\m1\us\word\draft-lab-text-lab-text-tr-w.docx.
- Annotated Comparison with the reference product (RP) PI received on February 26, 2021, available at the following link: \\CDSESUB1\evsprod\nda213895\0018\m1\us\114-labeling\annot-comp-drug-comp-listed-pi.pdf.

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/

DEBORAH E MYERS
07/28/2021 04:27:02 PM

VALERIE S VAUGHAN
07/28/2021 04:47:56 PM

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:	January 29, 2020
Requesting Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 213895
Product Name and Strength:	Vancomycin Injection, 5 grams/100 mL (50 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Xellia Pharmaceuticals ApS (Xellia)
FDA Received Date:	September 20, 2019, November 13, 2019, December 12, 2019, and January 8, 2020
OSE RCM #:	2019-1951
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for Vancomycin Injection, the Division of Anti-Infectives requested that we review the proposed Vancomycin prescribing information (PI), container label, and carton labeling, for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

On September 20, 2019, Xellia submitted the 505(b)(2) New Drug Application for NDA 213895.

On November 13, 2019, Xellia submitted an Amendment / Response to Information Request /Pharm/Tox that includes their correction of the typographical error regarding the amount of excipient PEG 400 (previously stated as 11.3 mg/vial has been corrected to 11.3 g/vial). Documents affected by this typographical error were revised and included in this submission.[a]

On December 12, 2019, Xellia submitted an Amendment / Response to Information Request / Clinical that includes information that no formal palatability testing of the proposed product, or stability with flavoring agents, have been performed.[b]

On January 8, 2020, Xellia submitted an Amendment / Response to Information Request that includes submission of updated prescribing information that has been amended to distinguish intravenous versus oral administration.[c]

On January 29, 2020, Xellia submitted an Amendment / Response to Information Request (DMEPA) that provides confirmation that the hanger, included in the proposed draft container label (see Appendix F.2), is separate from the container label and does not remove the text on the container label when hanger is pulled away from the container.[d]

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[a] Cover Letter: Amendment / Response to Information Request / Pharm/Tox (Vancomycin Injection NDA 213895). Copenhagen S (Denmark): Xellia Pharmaceuticals ApS; 2019 NOV 13. Available from: \\cdsesub1\evsprod\nda213895\0003\m1\us\1-2-cover-letter-seq-0003-amendment.pdf.

[b] Cover Letter: Amendment / Response to Information Request / Clinical (Vancomycin Injection NDA 213895). Copenhagen S (Denmark): Xellia Pharmaceuticals ApS; 2019 Dec 12. Available from: \\cdsesub1\evsprod\nda213895\0009\m1\us\12-cover\cover-0009.pdf.

[c] Cover Letter: Amendment / Response to Information Requests (Vancomycin Injection NDA 213895). Copenhagen S (Denmark): Xellia Pharmaceuticals ApS; 2020 JAN 08. Available from: \\cdsesub1\evsprod\nda213895\0012\m1\us\12-cover\cover-0012.pdf.

[d] Cover Letter: Amendment / Response to Information Request (DMEPA) (Vancomycin Injection NDA 213895). Copenhagen S (Denmark): Xellia Pharmaceuticals ApS; 2020 JAN 29. Available from: \\cdsesub1\evsprod\nda213895\0014\m1\us\12-cover\cover-0014-amendment.pdf.

3 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
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Label and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container label, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	As currently presented, the strength is stated as "5 g/100 mL" throughout the prescribing information (PI) does not include the quantity per milliliter statement, "50 mg/mL" that is currently	Inconsistent product strength statements could lead to confusion, as well as wrong strength medication errors.	Product strength statements should be consistent throughout all elements of the labeling (e.g., container, carton, and prescribing information).[e] To provide clarity, decrease the potential for wrong strength/dose

[e] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 380 - 381). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	included in Section 2, *Dosage and Administration, Preparation and Stability.*		medication errors, and to align with the strength statement (i.e., 5 g/100 mL (50 mg/mL)) currently in Section 2, *Dosage and Administration, Preparation and Stability,* and additionally has been recommended for inclusion on the revised container and carton labeling, we recommend the consistent use of the strength statement as "5 g/100 mL (50 mg/mL)" throughout the PI (i.e., Highlights of Prescribing Information, Section 3, *Dosage Forms and Strengths*, Section 11, *Description*, and Section 16, *How Supplied/Storage and Handling)*. For example, revise the current statements, "5 g/100 mL" to instead "5 g/100 mL (50 mg/mL)."
Highlights of Prescribing Information			
1.	As currently presented, under the header; *Dosage and Administration*, *For intravenous use, Adult Patients*, the unit of measure is abbreviated as, "g" and not written out (defined) as "grams", after the first mention of the abbreviation (i.e., "2 g	Abbreviations should be written out (defined), followed by the abbreviation itself enclosed by parentheses, with their first appearance in the document. Subsequent references to the abbreviation can be made just by the abbreviation letter(s) alone.	Following the Arabic numeral "2" replace the current "g" with "grams (g)" and following "0.5" replace the current "grams (g)" with "g." For example, "2 grams (g) divided either as 0.5 g every..." Alternatively, spell out the unit of measure (i.e., grams) throughout the document.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	divided either as 0.5 grams (g) every…").		
2.	As currently presented, under the header; *Dosage and Administration*, *For intravenous use,* the subheadings "Adult Patients" and "Pediatric Patients" are underlined, (b) (4)	Inconsistent labeling format may contribute to confusion that can result in medication error.	To provide consistency and clarity, underline the subheading (b) (4)
3.	As currently presented, under the header; *Dosage and Administration*, *For oral use*, both *Adult Patients* and *Pediatric Patients*, states the treatment duration as "7 to 10 days."	The shorter duration (7) in the range could be missed or misinterpreted because it is not followed by the appropriate unit of time (days).	To provide clarity and minimize the risk for misinterpretation, add the unit of time, "days" after the Arabic numeral "7." For example, "7 days to 10 days."
Full Prescribing Information – Section 2.2 *Dosage and Administration, Oral Administration*			
1.	As currently presented, the treatment duration reads "…for 7 to 10 days."	The shorter duration (7) in the range could be missed or misinterpreted because it is not followed by the appropriate unit of time (days).	To provide clarity and minimize the risk for misinterpretation, add the unit of time, "days" after the Arabic numeral "7." For example, "…for 7 days to 10 days."
Full Prescribing Information – Section 3 *Dosage Forms and Strengths*			
1.	As currently presented, the appropriate information to facilitate identification of the	A description of identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57(c)(4)(ii).	We recommend that the description of identifying characteristics of the dosage form, such as color (e.g., clear solution) or any other

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	dosage form is not included.		identifying characteristics, be added in accordance with 21 CFR 201.57(c)(4)(ii) (i.e., as stated in Section 16.1, *How Supplied*, "clear, colorless to light yellow or light brown solution").
Full Prescribing Information – Section 16 *How Supplied/Storage and Handling*			
1.	Under the subheading, 16.1, *How Supplied*, there is no space included between the Arabic numeral and the unit of measurement (i.e. "5g").	Presenting a dose, strength, or volume without a space between the numeral and unit of measurement can negatively impact readability.	To improve readability, add a space between the Arabic numeral "5" and the unit of measurement "g." For example, "…5 g/100 mL,…"
Container Label and Carton Labeling			
1.	We note the inclusion of the statement, "Vial stoppers (b) (4) natural rubber latex."		We defer to the Office of Pharmaceutical Quality (OPQ) for their assessment and to determine if the statement "Vial stoppers (b) (4) natural rubber latex." is appropriate.
2.	We note that this product should not be administered to pregnant women due to embryofetal toxicity associated with polyethylene glycol (PEG 400) and N-acetyl D-alanine (NADA) excipients.	This important safety information should be included on the container label and carton labeling to alert users that the product should not be used to prepare vancomycin doses that will be administered to pregnant women.	If the Division of Anti-Infectives (DIA) determines that this product should not be used to prepare vancomycin doses for pregnant women due to the embryofetal toxicity, the container label and carton labeling should include a warning statement accompanied by a graphic symbol.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			For example: Not for pregnant women 

Table 3. Identified Issues and Recommendations for Xellia Pharmaceuticals ApS (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the strength statement is "5 g per 100 mL", however the quantity per milliliter (i.e., 50 mg/mL) does not follow in close proximity.	The product strength is considered to be "critical information."[f] To avoid confusion, as well as wrong strength medication errors, the quantity per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by quantity per milliliter enclosed by parentheses.[g]	In close proximity to the strength per total volume, "5 g per 100 mL", add the strength per milliliter "50 mg/mL" enclosed by parentheses. For example, "5 g per 100 mL (50 mg/mL)."
Container Label			
1.	As currently presented, the format for the	Clearly define the expiration date will minimize confusion and risk	Identify the expiration date format you intend to use. FDA recommends that the human-

[f] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 134-151). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

[g] United States Pharmacopoeia (USP) General Chapter <7> Labeling.

Table 3. Identified Issues and Recommendations for Xellia Pharmaceuticals ApS (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	expiration date is not defined.	for deteriorated drug medication errors.	readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	As currently presented, the net quantity statement is missing.	The net quantity statement should appear on the PDP, but should be separated from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded).[h]	Add the net quantity statement to the principal display panel (PDP). For additional information, see 21 CFR 201.51.
Carton Labeling			

[h] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 461-463). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

Table 3. Identified Issues and Recommendations for Xellia Pharmaceuticals ApS (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	As currently presented, the intended location for the lot number and expiration date is not provided on the proposed carton labeling that was submitted.	The lot number statement is required on the carton labeling per 21 CFR 201.10(i)(1) and the product expiration date is also required on the carton labeling per 21 CFR 201.17.	Include the space notation for the lot number statement and expiration date. When determining this placement, please ensure that there are no other numbers located in close proximity to the lot number/expiration date that can be mistaken as the lot number/expiration date. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend that the human-readable expiration date on the container labels and carton labeling include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to

Table 3. Identified Issues and Recommendations for Xellia Pharmaceuticals ApS (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			separate the portions of the expiration date.
2.	As currently presented, the intended location of the human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) is not provided.	The drug package label must include the product identifier information (i.e., the NDC, serial number, lot number, and expiration date) in both the human-readable form and machine-readable, 2D data matrix barcode format.	We recommend you include the intended location of the machine-readable, 2D data matrix barcode product identifier, near the human-readable portion of the product identifier information (i.e., NDC: [insert product's NDC] SERIAL: [insert product's serial number] LOT: [insert product's lot number] EXP: [insert product's expiration date]). See draft guidance https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf (Lines 255 - 283).

5 CONCLUSION

Our evaluation of the proposed Vancomycin prescribing information (PI), container label, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Xellia Pharmaceuticals ApS so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Vancomycin that Xellia Pharmaceuticals ApS submitted on January 8, 2020, and the reference standard (RS) in Orange Book.

Table 4. Relevant Product Information for Reference Standard and Vancomycin		
Product Name	Vancomycin Hydrochloride for Injection, USP (ANDA 062663)	Vancomycin Injection (NDA 213895)
Initial Approval Date	March 17, 1987	N/A
Active Ingredient	vancomycin	vancomycin
Indication	For the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (β-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 hydrochloride for injection, USP is indicated for initial therapy when methicillin-resistant staphylococci are suspected, but after susceptibility data are available, therapy should be adjusted accordingly.	Intravenous treatment of: • Septicemia • Infective Endocarditis • Skin and Skin Structure Infections • Bone Infections • Lower Respiratory Tract Infections Oral treatment of: • *Clostridium Difficile*-associated diarrhea • Enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains)

	Effective in the treatment of staphylococcal endocarditis. The parenteral form of vancomycin hydrochloride may be administered orally for treatment of antibiotic-associated pseudomembranous colitis produced by C. difficile and for staphylococcal enterocolitis. Parenteral administration of vancomycin hydrochloride alone is of unproven benefit for these indications. Vancomycin is not effective by the oral route for other types of infections.	
Route of Administration	Intravenous Oral	Intravenous Oral
Dosage Form	lyophilized powder for injection	Injection
Strength	750 mg/vial	5 gram/100 mL (50 mg/mL)
Dose and Frequency	Adults with normal renal function: The usual daily intravenous dose is 2 grams divided either as 500 mg every six hours (b) (4) Each dose should be administered at no more than 10 mg/min, or over a period of at least 60 minutes, whichever is longer. Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose. Pediatric Patients: The usual intravenous dosage of vancomycin is 10 mg/kg per dose given every 6 hours. Each dose should be administered over a period of at least 60 minutes. Close monitoring of serum concentrations of	For intravenous use: • Administer Vancomycin Injection by intravenous infusion over 60 minutes or greater to reduce the risk of infusion reactions. • Adult Patients: 2 grams divided either as 0.5 grams (g) every 6 hours or 1 g every 12 hours • Pediatric Patients: 10 mg/kg per dose given every 6 hours • (b) (4) 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

	vancomycin may be warranted in these patients. Neonates: In pediatric patients up to the age of 1 month, the total daily intravenous dosage may be lower. In neonates, an initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the 1st week of life and every 8 hours thereafter up to the age of 1 month. Each dose should be administered over 60 minutes. In premature infants, vancomycin clearance decreases as postconceptional age decreases. Therefore, longer dosing intervals may be necessary in premature infants. Close monitoring of serum concentrations of vancomycin is recommended in these patients. Patients with Impaired Renal Function and Elderly Patients: Dosage adjustment must be made in patients with impaired renal function. DOSAGE TABLE FOR VANCOMYCIN IN PATIENTS WITH IMPAIRED RENAL FUNCTION (Adapted from Moellering et al.[3]) Creatinine Clearance mL/min / Vancomycin Dose mg/24 hr 100 / 1,545 90 / 1,390 80 / 1,235 70 / 1,080 60 / 925 50 / 770 40 / 620 30 / 465 20 / 310 10 / 155 For Oral Administration: Oral vancomycin is used in treating antibiotic-associated pseudomembranous colitis caused by C. difficile and for staphylococcal enterocolitis. Vancomycin is not effective by the oral route for other types of infections. The usual adult total daily dosage is 500 mg to 2 g given in 3 or 4 divided doses for	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 (b) (4) over 60 minutes, (b) (4) In premature infants, vancomycin clearance decreases as postconceptional age decreases. Therefore, longer dosing intervals may be necessary in premature infants. Close monitoring of serum concentrations of vancomycin is recommended in these patients. • Patients with Renal Impairment: Dosage adjustment must be made in patients with renal impairment. The initial dose should be no less than 15 mg/kg in patients with any degree of renal impairment. In the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Measure trough vancomycin

	7 to 10 days. The total daily dose in children is 40 mg/kg of body weight in 3 or 4 divided doses for 7 to 10 days. The total daily dosage should not exceed 2 g. The appropriate dose may be diluted in 1 oz of water and given to the patient to drink. Common flavoring syrups may be added to the solution to improve the taste for oral administration. The diluted solution may be administered via a nasogastric tube.	serum concentrations to guide therapy, especially in seriously ill patients with changing renal function. For functionally anephric patients, an initial dose of 15 mg/kg of body weight should be given to achieve prompt therapeutic serum concentration. A dose of 1.9 mg/kg/24 h should be given after the initial dose of 15 mg/kg. For oral use: • Adult Patients: 500 mg to 2 g given in 3 or 4 divided doses for 7 to 0 days. • Pediatric Patients: 40 mg/kg of body weight in 3 or 4 divided doses for (b)(4) to 10 days. • The total daily dosage should not exceed 2 g.
How Supplied	750 mg per vial Carton of 10 vials	5 gram/100 mL (50 mg/mL), pharmacy bulk package, packaged individually in cartons
Storage	Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].	Store at 15°C to 25°C (59° to 77°F), in original package, protect from light. Do not refrigerate or freeze.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 14, 2020, we searched for previous DMEPA reviews relevant to this current review using the term, "vancomycin." Our search identified 19 previous reviews[i,j,k,l,m,n,o,p,q,r,s,t,u,v,w,x,y,z,aa],

[i] Sheppard, J. Suitability Petition Review for Vancomycin for Injection (ANDA 062912). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 SEP 26. RCM No.: 2013-2401.

[j] Kolejian, S. Label and Labeling Review for Vancomycin Injection (NDA 050671/S-022). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 13. RCM No.: 2015-1997.

[k] Kolejian, S. Label and Labeling Review for Vancocin Capsules (NDA 050606/S-030). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 05. RCM No.: 2017-726.

[l] Kolejian, S. Label and Labeling Review Memo for Vancomycin for Injection (NDA 209481). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 16. RCM No.: 2016-1667.

[m] Miller, C. Postmarket Medication Error Review for Vecuronium Bromide for Injection and Vancomycin Hydrochloride for Injection (ANDAs 090243 and 065397). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUN 16. RCM No.: 2016-2569.

[n] Kolejian, S. Review Memo if Dosing Limitations for Vancomycin Injection Powder (ANDA 091532). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUN 28. RCM No.: 2017-1185.

[o] Kolejian, S. Proprietary Name Review for Firvanq (IND 123456 and NDA 208910). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 16. RCM No.: 2017-16834833 and 2017-15711523.

[p] Kolejian, S. Label and Labeling Review for Firvanq (NDA 208910). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 15. RCM No.: 2017-1530.

[q] Kolejian, S. Label and Labeling Review Memo for Firvanq (NDA 208910). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 11. RCM No.: 2017-1530-1.

[r] Kolejian, S. Label and Labeling Review for Vancomycin for Injection (NDA 209481). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 09. RCM No.: 2016-1667.

[s] Kolejian, S. Label and Labeling Review for Vancomycin for Injection (NDA 210274). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 26. RCM No.: 2017-552.

[t] Kolejian, S. Label and Labeling Review for Vancocin Capsules (NDA 050606/S-033). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 04. RCM No.: 2018-803.

[u] Kolejian, S. Label and Labeling Review Memo for Vancomycin for Injection (NDA 209481). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 29. RCM No.: 2016-1667-1.

[v] Kolejian, S. Label and Labeling Review for Vancomycin Injection (NDA 211962). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 15. RCM No.: 2018-1082.

[w] Hoste, S. Use-Related Risk Analysis Review for Firvanq (NDA 208910). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 SEP 25. RCM No.: 2018-1562.

[x] Myers, D. Label and Labeling Review Memo for Vancomycin Injection (NDA 211962). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 31. RCM No.: 2018-1082-1.

[y] Myers, D. Label Labeling and Packaging Review for Firvanq (NDA 208910/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 16. RCM No.: 2019-1394.

[z] Myers, D. Label Labeling and Packaging Review Memo for Firvanq (NDA 208910/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 15. RCM No.: 2019-1394-1.

[aa] Myers, D. Label and Labeling Review Memo for Firvanq (NDA 208910/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 10. RCM No.: 2019-1394-2.

and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX F. LABEL AND LABELING

F.1 List of Label and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[bb] along with postmarket medication error data, we reviewed the following Vancomycin labels and labeling submitted by Xellia Pharmaceuticals ApS.

- Container label received on November 13, 2019
- Carton labeling received on November 13, 2019
- Prescribing Information (PI) received on January 8, 2020
    - Track changes PI available at: \\cdsesub1\evsprod\nda213895\0012\m1\us\word\draft-lab-text-lab-text-tr-w.docx
    - Proposed (Draft) PI available at: \\cdsesub1\evsprod\nda213895\0012\m1\us\word\draft-lab-text-lab-text-cl-w.docx

F.2 Label and Labeling Images

Container label

(b) (4)

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[bb] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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