CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213895Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Summary Review

NDA #	213895
Applicant	Xellia Pharmaceuticals ApS
Date of Resubmission	February 26, 2021 (SDN#18)
PDUFA Goal Date	August 26, 2021
Proprietary Name / Established (USAN) names	Vancomycin Injection, USP*
Dosage forms/Strength	Solution/5g/100 mL Pharmacy Bulk Package
Proposed Indications	For intravenous administration: • Septicemia • Infective Endocarditis • Skin and Skin Structure Infections • Bone Infections • Lower Respiratory Tract Infections For oral administration: • *Clostridioides difficile*-associated diarrhea • Enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains)
Regulatory Action	Approval

* *No proprietary/trade name was proposed for the drug product.*

1. Background

Vancomycin is a tricyclic glycopeptide antibacterial drug that has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections including aerobic Gram-positive bacteria: *Corynebacterium* spp., *Enterococcu*s spp. (including *Enterococcus faecalis*) *Staphylococcus aureus* (including methicillin-resistant and methicillin-susceptible isolates) coagulase negative staphylococci (including *S. epidermidis* and methicillin-resistant isolates), *Streptococcus gallolyticus* (previously known as *Streptococcus bovis*), Viridans group streptococci, and *Clostridioides difficile*. Its mechanism of action results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis.

The Applicant, Xellia Pharmaceuticals ApS (Xellia), originally submitted NDA 213895 on September 20, 2019 as a 505(b)(2) application and received a Complete Response (CR) action from the Agency on March, 20, 2020, due to an inadequate assessment of leachables in the

proposed drug product. Please see the Multi-disciplinary NDA review (Unireview) signed into DARRTS on March 19, 2020, for additional details related to the original submission.

To note, the listed drug, Vancocin® Hydrochloride (Vancomycin Hydrochloride for Injection, USP) approved under ANDA 060180, is currently discontinued. A scientific bridge was established between the proposed product and ANDA 062663, the current Reference Standard (RS) for the *in vitro* bridging. The Applicant also provided a letter of cross-reference to their approved drug product, Vancomycin Injection USP, 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mg and 2 g/400 mL, NDA 211962. Of note, no clinical trials were conducted to support the original NDA.

As is the case for NDA 211962, this formulation of vancomycin contains the excipients N-acetyl-D-alanine (NADA) and polyethylene glycol 400 (PEG 400) that carry the potential risk of embryo-fetal toxicity based on findings in nonclinical studies conducted under NDA 211962. Given the potential risk of embryo-fetal toxicity, the labeling for this vancomycin product will include a Boxed Warning and a Warning regarding the risk of embryo-fetal toxicity.

2. Current Submission

Xellia submitted this NDA amendment on February 21, 2021, in response to the Agency's CR action. The proposed indications are the same as proposed in the original application. The Applicant's proposed dosing regimens are the same. For Intravenous Use: Adult Patients: 2 g divided either as 0.5 grams every 6 hours or 1 g every 12 hours, and Pediatric Patients (1 month and older): 10 mg/kg per dose given every 6 hours. For Oral Use: Adult Patients: 500 mg to 2 g given in 3 or 4 divided doses. Pediatric Patients: 40 mg/kg of body weight in 3 or 4 divided doses. The total daily dosage should not exceed 2 grams.

In this submission, the Applicant provided: (1) leachable information for the proposed drug product and some additional relatively minor CMC updates, (2) PK (Pharmacokinetic study-XEL1005.02) and population PK studies originally submitted to NDA 211962/S-009, Vancomycin Injection, that provided exposure data following administration of the Applicant's Vancomycin Injection, USP, to healthy volunteers in the PK study for the two excipients NADA and PEG 400, and (3) a reinterpretation of the nonclinical embryofetal development (EFD) study results, based on independent expert re-examination of skeletons of fetuses with reported skeletal abnormalities.

With regards to the proposed labeling, (b) (4)

On July 22, 2021, the Applicant confirmed that Ani's Vancocin (Vancomycin hydrochloride) oral capsules is the Listed Drug (NDA 50606) for the oral route of administration.

Product Quality/CMC:

The original NDA was recommended for CR by the Office of Pharmaceutical Quality (OPQ) review team due to the lack of leachable information for the container closure system proposed for the commercial drug product (refer to the OPQ Reviews # 1 and # 2 dated January 10, 2020 and March 9, 202, respectively). There were no other Product Quality deficiencies noted in the first review cycle. The current NDA resubmission includes mainly the leachable information for the proposed drug product container closure system, which has been found adequate by the CMC and Pharmacology/Toxicology teams. In addition, several relatively minor CMC updates have been also provided in the resubmission and found acceptable (e.g., extension of the drug substance retest period, additional stability data for the drug product primary stability batches, etc.).

This NDA, as amended, has provided sufficient and adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product, vancomycin injection. All manufacturing and testing facilities are deemed acceptable and an overall “Approve” recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on April 21, 2021. Therefore, this NDA is recommended for approval by the OPQ review team; for further details, refer to the OPQ Review # 3 dated July 30, 2021, in DARRTS.

Non-Clinical:

The Applicant submitted a leachables safety assessment in their resubmission to address the deficiencies outlined in the CR letter. The submission included assessment of the drug product for 8 and 16 months with and without packaging using semi-quantitative estimates of the leachables. Results from the analysis indicated that the elemental impurities were within acceptable limits. The analysis also identified five leachables of interest of which four were found above the safety concern threshold of 5 mcg/day: unknown (b) (4) det. by LC/DAD/MS @ RT of (b) (4) min, unknown (b) (4) det. by GC/MS DI @ RT of (b) (4) min, (b) (4). The Applicant provided information to indicate that these four leachables were not from the primary packaging material, and thus do not present a safety risk for administration of the drug product. The Applicant’s justification was found to be acceptable by the OPQ review team. Thus, no nonclinical studies were needed to qualify those leachables and the Applicant’s submission was considered adequate from a Pharmacology/Toxicology perspective.

In the resubmission package Xellia also submitted a summary of findings for the embryo-fetal developmental studies (EFD) conducted with PEG 400 and NADA in rats and rabbits, individual expert opinions, and the opinion of the Applicant’s pathology working group, to the current NDA 213895 to justify the Applicant’s proposed labeling language. The Pharmacology/Toxicology review team in DPT-ID, in consultation with the Agency’s Center for Drug Evaluation and Research Pharmacology/Toxicology Coordinating Committee-Reproductive and Developmental Toxicology Subcommittee (PTCC-RDTS), previously reviewed the reproductive and developmental toxicology data in the referenced NDA 211962. Overall, the Pharmacology/Toxicology review team and PTCC-RDTS did not agree with the Applicant’s or experts’ conclusions for the EFD rabbit studies with NADA and PEG 400 or with

the reassessment of fetal skeletal findings by their pathology working group. Based on these conclusions, the Pharmacology/Toxicology review team recommends language to describe the developmental findings for the EFD studies with NADA and PEG 400 in Section 8.1 of the labeling with updated exposure/safety margins for EFD findings to reflect AUC levels for PEG 400 and NADA obtained in non-pregnant healthy volunteers as recommended by the Clinical Pharmacology review team.

Following a Pharmacology/Toxicology Information Request, the Applicant provided a literature review of human bioavailability data for oral PEG 400 (b) (4) These data were found not to be adequate by the clinical pharmacology review team and were not used in the revised safety margin calculations. Specifically, the oral bioavailability information in the published literature was not estimated based on plasma drug exposures but rather urinary or fecal drug excretion. The Pharmacology/Toxicology review team recommends including language to describe the uncertainty and lack of information regarding the oral bioavailability of PEG 400 and NADA, respectively. Please refer to the Pharmacology/Toxicology review signed into DARRTS on 8/24/2021 for additional details. Additional edits to other sections of the labeling were made to be consistent with the Listed Drug labeling for NDA #050606.

Clinical Pharmacology:

There are no original clinical pharmacology studies conducted to specifically assess the pharmacokinetics of this Vancomycin Injection formulation. In this submission, the Applicant submitted the same pharmacokinetic (PK) and population PK studies that were submitted for the Vancomycin Injection clinical efficacy supplement (NDA 211962) but with an updated safety margin report. The PK data for vancomycin, NADA, and PEG 400 were derived from a single dose PK study (Study XEL.1005.02) in healthy subjects administered Vancomycin Injection (NDA 211962 formulation); meanwhile, the population PK model was used to fit the plasma concentration versus time data to predict AUC and Cmax values for each moiety at steady-state in both pregnant and non-pregnant subjects for Vancomycin Injection (NDA 211962 formulation). The safety margin report was updated to reflect the lower contents of excipients in the current Vancomycin Injection formulation compared to Vancomycin Injection (NDA 211962 formulation) after accounting for dose proportionality.

Additionally, the previous Clinical Pharmacology review team noted in NDA 211962/S-009 (Xellia's Vancomycin injection) their concerns that the population PK model used to generate the simulated AUC values in pregnant patients and subsequent safety margins did not appropriately describe the effect of renal function on the clearance of NADA and PEG 400. Since the Applicant did not provide additional information in this submission to clear any uncertainties in the pregnancy-associated pharmacokinetic changes of both excipients, we will continue to use the nonpregnant simulated excipient AUC values instead of the pregnant simulated excipient AUC values when determining the safety margins. .

Clinical and Labeling Review:

The clinical review of the safety update for vancomycin injection (both for intravenous and oral use) did not identify any new safety signals related to vancomycin. In addition, the medical

officer reviewed the safety data in the Applicant's pharmacokinetic study (XEL 1005.02) and no new safety concerns were noted.

The submitted prescribing information included new safety information related to the risk of severe dermatologic adverse reactions [i.e., toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and linear IgA bullous dermatosis (LABD)]. These safety labeling changes were approved on January 29, 2021, and are included in the WARNINGS AND PRECAUTIONS (5), subsection 5.4 regarding Severe Dermatologic Reactions; ADVERSE REACTIONS (6), Post Marketing Experience (6.2) subsection regarding Skin and Subcutaneous Tissue Disorders; and 17 PATIENT COUNSELING INFORMATION under Serious Dermatologic Reactions.

The Division of Anti-Infectives and the OND Labeling Policy Team in consultation with the Division of Pediatric and Maternal Health (DPMH) recommended labeling for the intravenous and oral formulation of this vancomycin product to be similar to the recently approved NDA 211962/S-009, Vancomycin Injection in retaining the Boxed Warning and Warnings and Precautions (5.1) with revised language related to the excipients PEG 400 and NADA. The title ("Potential Risk of Exposure to Excipient During the First or Second Trimester of Pregnancy") and the text in the Boxed Warning, and Warnings and Precautions (5.1) have been updated to further communicate the risks of this vancomycin formulation as compared with other formulations of vancomycin that do not contain PEG 400 and NADA.

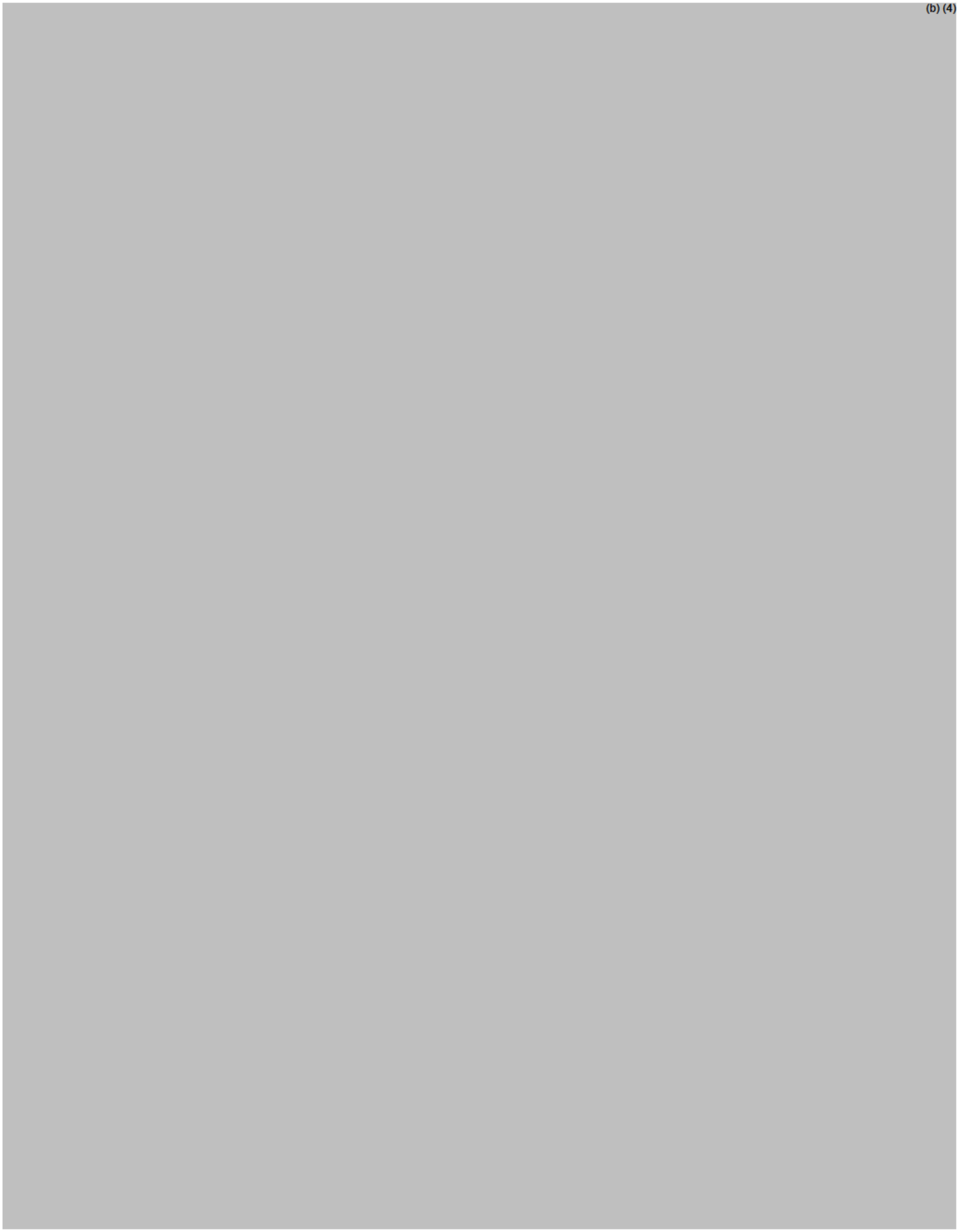
It was noted during the review that the potential adverse developmental effects of PEG 400 with oral administration are unknown as the oral bioavailability of PEG 400 is uncertain. The oral bioavailability of PEG 400 in the published literature as provided by the applicant, was not estimated based on plasma drug exposure but based on urinary or fecal drug excretion. Thus, the information in the literature was deemed insufficient to include a clinical PEG 400 oral bioavailability value in the labeling. Although the oral bioavailability of NADA is also unknown, based on animal studies, there is no concern for human embryo-fetal toxicity with NADA exposure during pregnancy from either route of administration. The Division, the OND Labeling Policy Team, and DPMH recommended that only the PEG 400 be discussed in the Boxed Warning with cross-referencing to subsections 5.1 and 8.1.

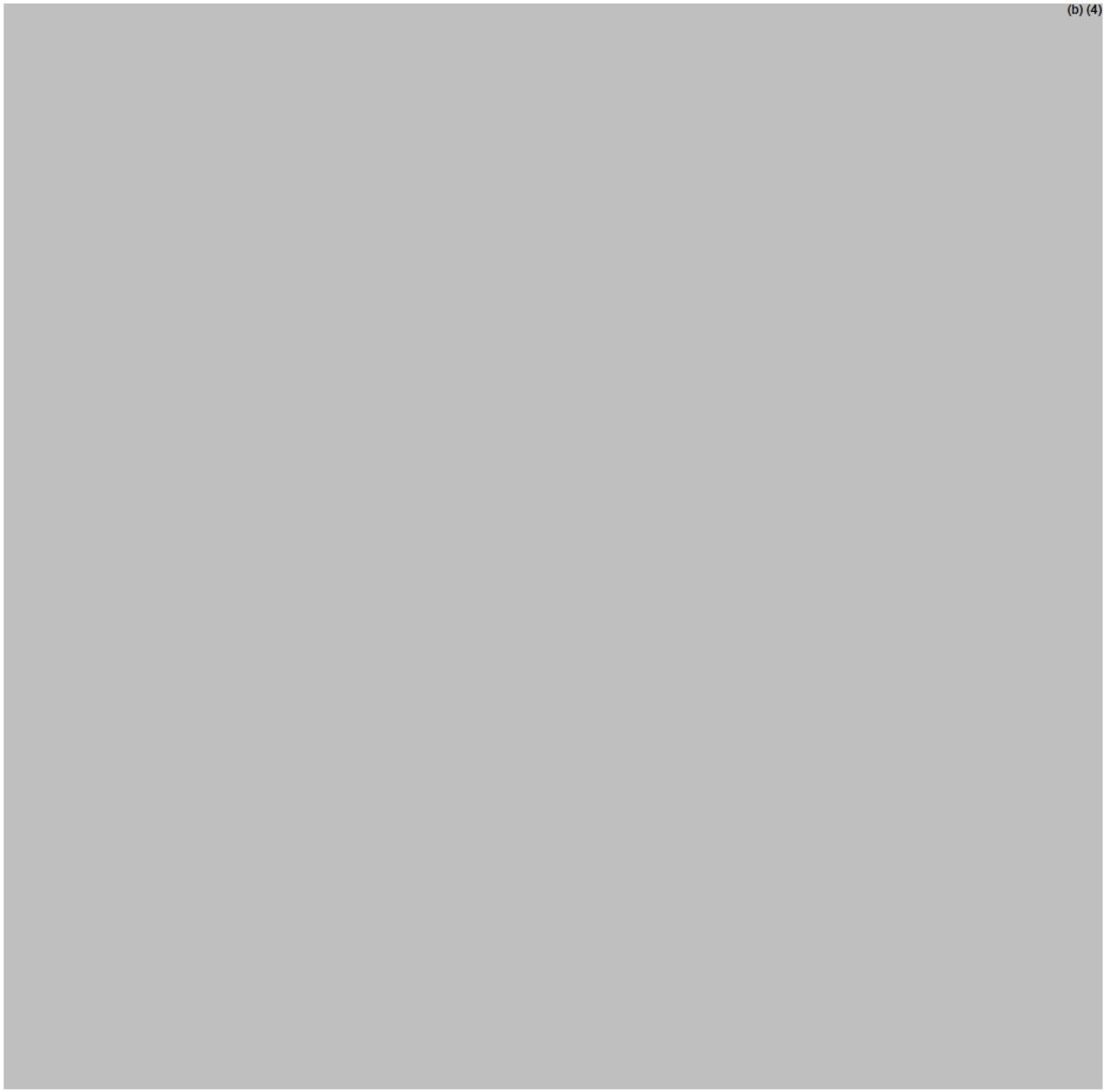
The following table provides a high-level summary of the labeling changes.

Table 1: Summary of High-level Labeling Changes to the Prescribing Information (PI)

Reviewer's Comment: Please note that the reviewer's proposed significant labeling changes (below) are high level changes that were changed from the previous recommendations in the Unireview signed into DARRTS on March 19, 2020.

(b) (4)





Significant Labeling Changes to the Carton and Container Labeling
The revision of the product title to include the oral route of administration was also applied to the carton and container labeling based on the recommendation of DMEPA and OPQ. Additionally, a warning in a box that included only the header of the Boxed Warning was also added to the carton and container labeling.

Please see the OPQ and DMEPA reviews for further details.

3. Regulatory Action:

This New Drug Application (NDA 213895) for Vancomycin Injection, USP, (Solution/5g/100 mL Pharmacy Bulk Package) will receive an approval action.

Reviewers:
Clinical: Alma Davidson, MD, CPH
Clinical Team Leader: Peter Kim, MD, MS
Cross-Discipline Team Leader: Dorota Matecka, PHD
Deputy Division Director: Dmitri Iarikov, MD, PHD

Signatures: *{See appended electronic signature page}*

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/

CHRISTOPHER L SMITH
08/26/2021 08:20:32 AM

ALMA C DAVIDSON
08/26/2021 09:03:08 AM

PETER W KIM
08/26/2021 09:06:33 AM

DOROTA M MATECKA
08/26/2021 10:58:45 AM

DMITRI IARIKOV
08/26/2021 11:04:35 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA ASSESSMENT AND EVALUATION

Application Number*:	NDA 213895
Supporting Document Number/s:	18
CDER Receipt Date:	02/26/2021
Sponsor:	Xellia Pharmaceutical APS Dalsandsgade 11 2300 Copenhagen S, Denmark
Product:	Vancomycin Injection, 5 g/100 mL
Pharmacologic Class:	Glycopeptide antibiotic
Indication:	Treatment of septicemia, infective endocarditis, skin and skin structure infections, bone infections, lower respiratory infections, pseudomembranous colitis caused by C. difficile and staphylococcal enterocolitis
Clinical Review Division:	Division of Anti-Infectives (DAI)
Pharm/Tox Division	Division of Pharm/Tox for Infectious Diseases (DPT-ID)
Reviewer:	Madisa Macon, MPH, PhD
Supervisor/Team Leader:	Terry Miller, PhD
Project Manager:	Christopher Smith, PharmD, MPH, BCPS, RAC
Reviewer Completion Date:	August 23, 2021

Template Version: Sep 11, 2020

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Executive Summary

Introduction

Xellia Pharmaceuticals ApS previously submitted their package for NDA 213895 to the Division on 9/29/2019. Following review, the Division sent a Complete Response to the Applicant (03/20/2020) due to a lack of a drug product leachable assessment. On 02/26/2021, the Applicant resubmitted their NDA and included information to address the issues outlined in the Complete Response.

In their CR letter response sent to the Agency, the Applicant submitted a leachable safety assessment to address the deficiencies in the CR letter. Their assessment included analysis of the drug product and glass vials used to package the drug product from report "Safety assessment and justification of extractables from (b) (4) stoppers and 100mL USP (b) (4) glass vials", Report No. 648-SCR Revision 1, Report 772-SCR Revision 2.0, and Report 933-SCR Revision 0.0. The analysis included assessment of the drug product with and without packaging following 8 and 16 months. Analysis of the drug product following 8 and16 months showed that the elemental impurities were at acceptable levels. In addition, five leachables of interest were identified. Of the five, four were found to be above the safety concern threshold of 5 mcg/day. The Applicant provided a justification for the presence of these leachable (b) (4) This justification was found to be acceptable by the Chemistry and Manufacturing Controls (CMC) review team. As there were no leachables of concern, the Applicant did not conduct any new nonclinical studies. Therefore, from a Pharmacology/Toxicology perspective, the Applicant provided adequate information to qualify the leachables for safety and have fully addressed the deficiencies described in the CR letter.

Additionally, the Applicant submitted new language for Section 8.1 of the drug labeling. The Applicant consulted reproductive toxicology experts and submitted their reviews, a reassessment of the nonclinical embryo-fetal developmental (EFD) studies conducted to qualify the safety of the excipients NADA and PEG 400, in addition to a human PK simulation analysis of PEG 400 and NADA. The EFD studies, their expert reviews, and the reassessment were previously reviewed under NDA 211962. The PK simulation of PEG 400 and NADA with this drug product based on measured PK of PEG 400 and NADA following IV administration of vancomycin for NDA 211962 (which contains the excipients PEG 400 and NADA at higher levels) in healthy human volunteers and reviewed by the Clinical Pharmacology review team. Overall, the Pharmacology/Toxicology review team in consult with the experts in the Pharmacology/Toxicology Reproductive and Developmental Toxicology Subcommittee did not agree with the Applicant's conclusions or with the reassessment of fetal skeletal findings by the Applicant's pathology working group. Based on these conclusions, the Pharmacology/Toxicology review team in concert with the Clinical, Clinical Pharmacology, and DPMH review teams recommended language to describe the

developmental findings for the EFD studies with NADA and PEG 400 in Section 8.1 of the labeling, with updated exposure/safety margins using simulated PK values for PEG 400 and NADA in non-pregnant healthy volunteers as recommended by the Clinical Pharmacology review team. In addition, upon request the Applicant provided a literature review of human bioavailability data for oral PEG400 (b) (4) These data were found not to be adequate by the clinical pharmacology review team and were not used in the revised safety margin calculations. The Pharmacology/Toxicology review team recommended including language in the drug labeling to describe the uncertainty and lack of information regarding the oral bioavailability of PEG 400 and NADA, respectively.

Recommendations

Approvability

The Applicant has adequately addressed the deficiencies noted in the CR letter and has provided sufficient nonclinical safety information in the NDA for Xellia Vancomycin to support its approval for marketing in the U.S. Recommendations for language in the pharmacology/toxicology relevant sections of the labeling were provided to the Applicant.

Labeling

Prescribing information

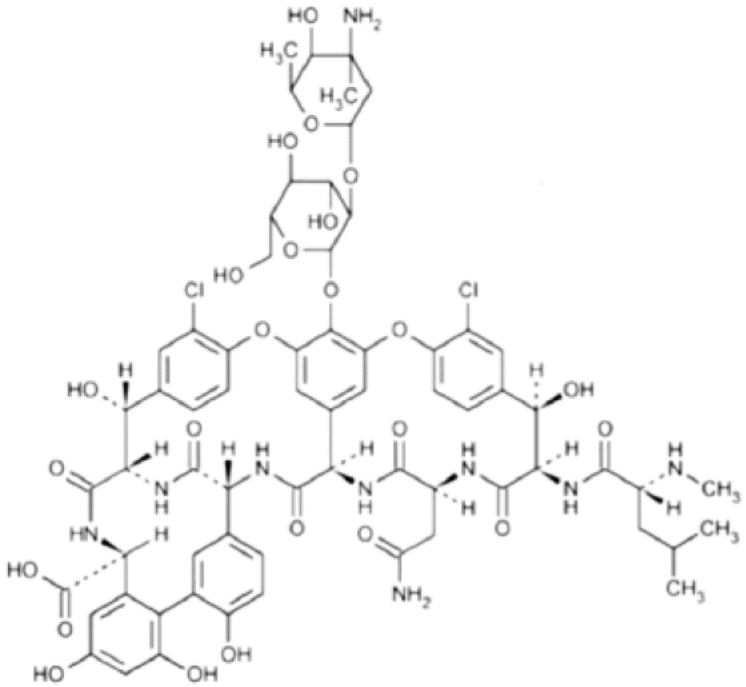
1. A Boxed Warning and Warning was included in the product labeling by the clinical review team due to the risk of embryo-fetal effects from the excipient PEG 400 found in the formulation of Xellia Vancomycin for both intravenous and oral administration. Based on intravenous embryo-fetal findings from nonclinical safety studies with PEG 400, inclusion of the Boxed Warning and Warning is supported from a Pharmacology/Toxicology perspective.

Section 8.1 Pregnancy-Risk Summary

1. The text (b) (4) was removed from the Risk Summary to comply with current PLLR language recommendations.
2. Text was added in the Risk Summary to reflect the Warning for embryo-fetal effects in the Boxed Warning and Warning Section of the labeling.
3. Text was added to Section 13.1 to include additional genotoxicity information from the listed drug labeling for Vancocin.

Nonclinical Summary

Drug Information+

Type of Product:	Vancomycin Injection 5g/100 mL
Code/ Generic Name:	N/A; Vancomycin
Chemical Name (optional):	(Sa)-(3S,6R,7R,22R,23S,26S,36R,38aR)-44-{[2-O-(3-amino-2,3,6-trideoxy-3-C-methyl-α-L-lyxo-hexopyranosyl)-β-D-glucopyranosyl]-oxy}-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5, 6,7,23,24, 25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[(2R)-4-methyl-2-(methylamino]valeramido]-2,5,24,38,39-pentaoxo-22H-8,11 : 18,21-dietheno-23,36-(iminomethano)-13,16 : 31,35-dimetheno-1H,16H-[1,6,9]-oxadiazacyclohexadecino-[4,5-m][10,2,16]-benzoxadiazacyclotetracosine-26-carboxylic acid.
CAS#	CAS:1404-90-6
Structure or Biochemical Description:	
Molecular Formula/ Molecular Weight:	$C_{66}H_{75}Cl_2N_9O_{24}$/ 1449.265 g/mol (base)
Comment on Excipients:	No novel excipients for IV; NADA is a novel excipient for the oral administration of this product
Comment on Impurities:	The novel impurity (b) (4) was adequately qualified for safety with nonclinical studies.

505(b)(2):	Y
Listed Drug (s):	ANDA 060180: Vancocin Injection, Ani Pharmaceuticals; NDA 050606: Vancocin Capsule, Ani Pharmaceuticals
Referenced Standard:	ANDA 062663: Vancomycin Injection, Fresnius Kabi
Referenced Drug:	USA NDA 211962: Vancomycin Injection RTU, Xellia Pharmaceuticals APS

1 Background

1.3 Regulatory History

Xellia Pharmaceuticals ApS previously submitted their package for NDA 213895 to the Division on 9/29/2019. Following review, the Division sent a Complete Response to the Applicant (03/20/2020) due to a lack of a drug product leachable assessment. On 02/26/2021, the Applicant resubmitted their NDA after addressing the Division concerns for a Complete Response. In their CR letter response sent to the Agency, the Applicant submitted a leachable safety assessment of the drug product with and without packaging following 16 months of storage at 25°C±2°C/60%RH±5%RH in upright and inverted position and one scale up batch after 8 months.

1.2 Relevant INDs, NDAs, BLAs or DMFs

ANDA 060189, Ani Pharmaceuticals, (Listed Drug)
NDA 050606, Ani Pharmaceuticals, (Listed Drug)
ANDA 062663, Fresenius Kabi, (Reference Substance; Biocompatibility Drug Product)
NDA 211962 Xellia Pharmaceuticals (Qualitatively Similar Drug Product)
DMF (b) (4)

1.3 Previous Reviews Referenced

Application	Reviewer	Date in DARRTS	Notes
NDA 211962	Dr. Macon	02/12/2019	Unireview Section 4 Nonclinical Pharmacology/Toxicology
NDA 213895	Dr. Macon	03/29/2020	Unireview Section 4 Nonclinical Pharmacology/Toxicology
NDA 211962	Dr. Macon	05/25/2021	Efficacy Review

1.4 Nonclinical Deficiencies from the Complete Response Letter (03/20/2020)

1. Qualify all applicable leachables for the proposed vancomycin drug product. The acceptability of the proposed stopper cannot be determined until the identity and the safety profile of the leachables are considered acceptable from a nonclinical perspective. The data from the leachables study have not been submitted to the

NDA.

2. Provide a comprehensive toxicological risk assessment (e.g., local toxicity, systemic toxicity, mutagenicity, carcinogenicity, reproductive toxicity) for any leachable that exceeds 5 mcg/day. From a genetic toxicology perspective, 120 mcg/day is considered an acceptable daily intake of any leachable that contains a structural alert for mutagenicity for an acute indication (≤ 1 month). The risk assessment should be based on the levels of leachables detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Additional nonclinical studies may be required to qualify any leachables identified that exceed the safety thresholds. Refer to the publication "The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and Nonclinical Ophthalmic Drug Product (PODP)", and the ICH M7 Guideline on Genotoxic Impurities for guidance on the evaluation of impurities relative to their genotoxic potential.

1.5 Applicant's Response to the Complete Response Letter:

In their CR letter response sent to the Agency, the Applicant submitted a leachable safety assessment to address the deficiencies in the CR letter. Their assessment included analysis of the drug product and glass vials used to package the drug product from report "Safety assessment and justification of extractables from (b) (4) stoppers and 100mL USP (b) (4) glass vials", Report No. 648-SCR Revision 1, Report 772-SCR Revision 2.0, and Report 933-SCR Revision 0.0. The analysis included assessment of the three batches of the drug product with and without packaging following 16 months of storage at 25°C±2°C/60%RH±5%RH in upright and inverted position and one scale up batch after 8 months. Analysis of the drug product following 8 and 16 months are below in Table 1:

Table 1. Comparison of extractable results obtained on vials and screening leachable results obtained on three Xellia`s exhibit batches after about 16 months of storage at long term condition.

All elemental impurities were found to be below the limit of quantitation or below levels of concern. The Applicant provided additional justification for the levels of (b) (4) as they are classified as (b) (4) elemental impurities in the ICH Q3D (R1) guidance. The levels of (b) (4) in the drug product batches are provided in Table 2 below.

Table 2. Levels of elemental detected in Vancomycin Injection 5g/100mL drug product

Per ICH Q3D (R1), the permitted daily exposure (PDE) of (b) (4) mcg/day, respectively. The levels of those two elemental impurities were well below their PDEs in the Applicant's analysis, thus the level of elemental impurities in the drug product were adequately qualified for safety from a Pharmacology/Toxicology perspective.

The Applicant also conducted a screening leachable study conducted by (b) (4) (Report No. 648-SCR Revision 1/Attachment 2) on three batches of the drug product with and without packaging following 16 months of storage at 25°C±2°C/60%RH±5%RH in upright and inverted position and one scale up batch

after 8 months. There were five leachables of interest that were identified by the analysis (shown in Table 3 below).

Table 3. Levels of leachables detected with LC/DAD/MS and GC/MS DI in Vancomycin Injection 5g/100mL drug product

Of the five leachables identified above, four were found to be above the safety threshold concern of 5 mcg/day: (b) (4) det. by LC/DAD/MS @ RT of (b) (4) min, unknown (b) (4) det. by GC/MS DI @ RT of (b) (4) min, (b) (4) . An additional screening leachable study was conducted to investigate the levels of the four leachables. These four leachables were (b) (4) were not considered to be from the primary packaging material per the Applicant. This data and justification were reviewed by the CMC reviewer, Dr. George Lunn, and found to be acceptable. No additional nonclinical studies for leachables were conducted by the Applicant. However, the Applicant provided additional data to support the levels of (b) (4) found in samples. The Applicant concluded that the levels of (b) (4) in the samples would be unlikely to present a safety concern at maximum daily exposures. Based on the recommendations by the CMC reviewer, the Applicant's submission was considered provided adequate safety for the leachable in this drug product from a Pharmacology/Toxicology perspective.

*(**Reviewer's Comments:** The additional justification provided by the Applicant to qualify levels of (b) (4) was not reviewed by this reviewer as the CMC reviewer considered the Applicant's leachable justification to be acceptable.)*

2 Reproductive and Developmental Toxicology

No studies were conducted with this Xellia Vancomycin product to assess its potential reproductive or developmental toxicity. The Applicant submitted nonclinical embryofetal development studies for two of the excipients NADA and PEG 400 in Xellia Vancomycin

in the first NDA submission. These studies were previously reviewed in full and found adequate by Dr. Madisa Macon for the referenced NDA 211962. Summaries of these studies are included below.

In the resubmission package, the Applicant also submitted a reassessment of the findings for the embryo-fetal toxicity studies conducted for NADA and PEG 400 based on individual expert opinions and the collective opinions of a pathology working group (See section 2.1.4 below). The reassessment was reviewed in full by the Pharmacology/Toxicology review team, in concert with the Agency's Center for Drug Evaluation and Research Pharmacology/Toxicology Coordinating Committee-Reproductive and Developmental Toxicology Subcommittee (PTCC-RDTS) for the referenced NDA 211962. A summary of the Division's study conclusions is also included below.

2.1 Previously Submitted Toxicology Studies

(Refer to multi-disciplinary Unireview for NDA 211962 submitted into DARRTS 2/14/2019 for more information)

2.1.1 Study Title: N-acetyl-D-alanine (NADA): Study for Effects on Embryo-Fetal Development in New Zealand White Rabbit by Intravenous Infusion Administration/ LF72KH

Key Study Findings

- NADA was not well tolerated in pregnant rabbits administered 3780 mg/kg with neurological and respiratory adverse clinical signs. Excessive urination and drinking were also noted in the 1680 mg/kg group. Fetal exposure to NADA IV led to fetal major cardiovascular abnormalities and major and minor skeletal abnormalities at ≥ 1680 mg/kg.
- The NADA no observed adverse effect level (NOAEL) for maternal toxicity was 1680 mg/kg and embryofetal development was 560 mg/kg.
- A dose of 1680 mg/kg NADA is equivalent to 545 mg/kg HED based on body surface area comparison (approximately 6 times higher than 90.5 mg/kg NADA in a 60 kg human receiving the maximum dose of Xellia Vancomycin Injection at 2 g); 560 mg/kg NADA is equivalent to 181 mg/kg Human Equivalent Dose (HED) based on body surface area comparison (approximately 2 times higher than 90.5 mg/kg NADA in a 60 kg human receiving the maximum dose of Xellia Vancomycin Injection at 2 g).

2.1.2 Study Title: N-acetyl-D-alanine (NADA): Study for Effects on Embryo-Fetal Development in Sprague Dawley [Crl:CD(SD)] rat by Intravenous Infusion Administration/ PT59XC

Key Study Findings

- No major effects on maternal health related to NADA exposure; in fetuses, NADA increased full litter resorption at 3780 mg/kg, increased fetal developmental anomalies including misshapen margin scapulae, interparietal fissures at ≥1680 mg/kg, and malpositioned testis at 3780 mg/kg NADA.

- The NOAEL for maternal and embryofetal toxicity was 1680 mg/kg NADA (approximately 3 times higher than 90.5 mg/kg NADA in a 60 kg human receiving the maximum dose of Xellia Vancomycin Injection at 2 g based on body surface area comparisons).

2.1.3 Study Title: PEG 400: Embryo-fetal Toxicity Study in the New Zealand White Rabbit /DG90YB

Key Study Findings

- No major effects on maternal health at any dose; in fetuses, increases in spinal malformation including lumbar and thoracic scoliosis and increased delayed or incomplete ossification of cranial fontanelles, pubes, epiphyses, and talus bones at 2000 mg/kg PEG 400.
- The maternal toxicity no observable adverse effect level (NOAEL) was 2000 mg/kg PEG 400; the embryofetal toxicity NOAEL was 500 mg/kg PEG 400
- 2000 mg/kg is 648 mg/kg HED (approximately 4.8 times higher than 135.3 mg/kg PEG 400 in a 60 kg human receiving the maximum dose of Xellia Vancomycin Injection at 2 g based on body surface area); 500 mg/kg PEG 400 is 162 mg/kg HED (approximately 1.2 times higher than 135.3 mg/kg PEG 400 in a 60 kg human receiving the maximum dose of Xellia Vancomycin Injection at 2 g based on body surface area).

*(**Reviewer's Comments**: It is possible that the embryo-fetal skeletal malformations observed in this study were due to the large amount of drug administered rather than the direct toxicity of PEG 400. In general, the maximum dose recommended for EFD studies are 1000 mg/kg, due to feasibility issues. At 1000 mg/kg PEG 400, the safety multiples would be slightly above 2 times above the assumed amount of PEG 400 in maximum dose of vancomycin at 2 grams in a 60 kg human. Thus, the Sponsor/Applicant conducted the study with higher doses of PEG 400 to achieve higher safety multiples to the human clinical dose. Following additional review of the current literature on PEG 400 (or PEG) toxicity, it is assumed that the findings of fetal skeletal malformation are real. In his chapter on PEG in FDA approved products, Webster et al. (2009)[1] suggests that the general renal toxicity of PEG 400 is likely to one of its metabolites, glycolic acid (GA). It is also assumed that GA is responsible for the presentation of acidosis in patients exposed to high doses via any route of exposure[1]. In a EFD study in rats, oral exposure to ethylene glycol and GA were shown to lead to fetal axial skeletal malformations and other fetal malformations[2]. This suggests that the fetal skeletal malformations observed in the EFD rabbit study with PEG 400 are likely related to PEG 400 exposures, albeit indirectly through its metabolites, and not related to a generic high volume/concentration of a chemical. It is also possible that these observed*

[1] Webster R., Elliott V., Park B.K., Walker D., Hankin M., Taupin P. (2009) PEG and PEG conjugates toxicity: towards an understanding of the toxicity of PEG and its relevance to PEGylated biologicals. In: Veronese F.M. (eds) PEGylated Protein Drugs: Basic Science and Clinical Applications. Milestones in Drug Therapy. Birkhäuser Basel. https://doi.org/10.1007/978-3-7643-8679-5_8

[2] Carney E.W., Freshour N.L., Dittenber D.A., Dryzga M.D. (1999) Ethylene Glycol Developmental Toxicity: Unraveling the Roles of Glycolic Acid and Metabolic Acidosis. Toxicological Sciences. 50: 117-126.

findings were due to PEG 400 impurities (b) (4)

2.1.4 Applicant's Reassessment of Embryo-fetal Toxicity findings for PEG 400 and NADA

After the issues in the Complete Response were addressed, the Applicant also submitted a reassessment of the findings for the embryo-fetal toxicity studies conducted for NADA and PEG 400 based on individual expert opinions and the collective opinions of a pathology working group regarding. This reassessment of the EFD data with PEG400 and NADA were reviewed in full by the Pharmacology/Toxicology review team, in concert with the Agency's Center for Drug Evaluation and Research Pharmacology/Toxicology Coordinating Committee-Reproductive and Developmental Toxicology Subcommittee (PTCC-RDTS) for the referenced NDA 211962. The Pharmacology/Toxicology review team and PTCC-RDTS did not agree with the Applicant's or experts' conclusions for the EFD rabbit studies with NADA and PEG 400 or with the reassessment of fetal skeletal findings by their pathology working group. The Pharmacology/Toxicology review team recommends that the NOAEL values remain the same as the original conclusions for NDA 211962 (b) (4) . Following internal discussion and in consult with DPMH, language in Section 8.1 was edited to 1) include language in the Risk Summary and Animal Data that is similar to the referenced NDA 211962 but 2) remove language related (b) (4) 3) include exposure margins values for the developmental findings based on AUC levels simulated from measured excipient exposures in non-pregnant healthy volunteers administered intravenous Vancomycin RTU (which contains PEG 400 and NADA) as recommended by the Clinical Pharmacology review team, and 4) include language to describe the uncertainty and unknown oral bioavailability of PEG 400 and NADA, respectively.

Please refer to the full review under NDA 219962 signed into DARRTS on 05/24/2021 for more information.

(Reviewer's Comments: *Based on the pharm/tox review in consult with the PTCC CDER subcommittee, the Division determined the Applicant has not provided sufficient information* (b) (4)

(b) (4)

(b) (4)

. There was no disagreement between the Division and the Applicant concerning the NOAEL for the EFD NADA study in rats (1680 mg/kg). In agreement with the recommendations of internal experts on the CDER reproductive toxicology subcommittee, the pharm/tox relevant sections of the labeling for NDA 211962 were not changed in response to the TWG assessment. Therefore, the pharmtox relevant section of the labeling for NDA 213895 will not be changed in response to the TWG assessment.

The Applicant submitted a PK study of Xellia Vancomycin Injection administered to non-pregnant healthy volunteers to measure the systemic exposures of vancomycin, NADA, and PEG 400 following a 500 mg dose of Xellia Vancomycin every 6 hours or 1000 mg dose of Xellia Vancomycin every 12 hours. The Applicant also developed a PK simulation model for PEG 400 and NADA in pregnant women based on published data that suggest pregnant women metabolize and renally clear pharmaceuticals faster than non-pregnant patients. Both submissions were reviewed by the Clinical Pharmacology Review Team. A summary of the exposure/safety margins to the rat and rabbit EFD with NADA and PEG 400 studies are provided below in Table 4.

Table 4. Summary of Exposure/Safety Margins for AUC0-24h for Non-Pregnant Patients After Intravenous Administration of the Labelled Dose of Vancomycin Injection 50 mg/mL

Excipient	Species	Animal Dose (mg/kg/day)	Animal AUC (mcg*h/mL)	Exposure Margins Vancomycin Injection 5 g/100mL 1gram q 12h Non-Pregnant Patients
NADA	Rabbit	560 (NOAEL)	4050	31.6 X
		1680 (LOAEL)	12300	96.1 X
	Rat	1680 (NOAEL)	3370	26.3 X
		3780 (LOAEL)	7480	58.4 X
PEG 400	Rabbit	500 (NOAEL)	935	2.3 X
		1000 (LOAEL)	2250	5.5 X
		2000	5470	13.4 X

The Division sent an Information Request to the Applicant to support the human PK of the two excipient PEG 400 and NADA based on oral bioavailability of the substances (Sent to Applicant on 7/14/2021). The Applicant responded to the request with oral bioavailability data of PEG 400 from published literature. There were no data submitted to support the oral bioavailability of NADA. Based on the submitted information, the Applicant believed that the oral bioavailability of PEG 400 is between 20-40% and assumed the oral bioavailability of NADA is 100% of intravenous administration. The

Applicant calculated the oral exposure/safety margins to the embryo-fetal toxicity findings as follows:

Table 5. Applicant Summary of Exposure/Safety Margins for AUC0-24h for Non-Pregnant Patient After Oral Administration of the Labelled Dose of Vancomycin Injection 50 mg/mL (Assuming 100% oral bioavailability of NADA and 40% oral bioavailability of PEG 400)

Excipient	Species	Animal Dose (mg/kg/day)	Animal AUC (mcg*h/mL)	Exposure Margins Vancomycin Injection 5g/100 mL 1 gram q 12h Non-Pregnant Patients
NADA	Rabbit	560 (NOAEL)	4050	31.6 X
		1680 (LOAEL)	12300	96.1 X
	Rat	1680 (NOAEL)	3370	26.3 X
		3780 (LOAEL)	7480	58.4 X
PEG 400	Rabbit	500 (NOAEL)	935	5.7 X
		1000 (LOAEL)	2250	13.8 X
		2000	5470	33.5 X

The Clinical Pharmacology Review Team reviewed the submitted information and determined that the quality of the data was not adequate to support the Applicant's conclusions regarding the reduced oral bioavailability of PEG 400. Based on the recommendations from the Clinical Pharmacology review team and in the absence of any additional information, it is assumed that the oral bioavailability of PEG 400 is 100%. Therefore, for labeling purposes, the exposure/safety margins to the IV EFD effects will be as listed as shown in Table 4.

*(**Reviewer's Comments**: Regarding the boxed warning, the exposure/safety margins to the embryo-fetal effects due to NADA administered IV or orally are above the threshold of concern, as described in ICH Guidance S5(R3). Therefore, the nonclinical data support exclusion of NADA from the boxed warning from a pharmacology/toxicology perspective. The NOAEL for NADA is 32 times higher, and the effect level is 96 times higher than the assumed NADA exposures at the maximum dose of vancomycin based on AUC levels in animals and AUC levels in the human PK simulations for this vancomycin product. The exposure/safety margins to the embryo-fetal effects due to PEG 400 administered IV or orally are within the threshold of concern and thus the nonclinical data support inclusion of PEG 400 in the boxed warning from a pharmacology/toxicology perspective. The NOAEL for PEG 400 is ~2.3 times higher and the effect level is ~13.4 times higher than the assumed PEG 400 exposures at the maximum recommended dose of vancomycin based on AUC levels in animals and AUC levels in the human PK simulations for this vancomycin product. There are published*

reports that suggest that the human oral bioavailability of PEG 400 is below 100%[3,4] thus it is possible that the pregnancy risk to EFD from PEG 400 exposures is lower from oral administration of this product compared to IV. However, those reports were reviewed by the Clinical Pharmacology review team and deemed to be inadequate. Thus, the exposure/safety margins to the EFD effects due to PEG 400 from oral administration of Xellia Vancomycin are the same as the IV exposure/safety margins.)

[3] Schaffer C.B., Critchfield F.H., Nair, J.H., III. (1950) The Absorption and Excretion of a Liquid Polyethylene Glycol. J Am Pharm Assoc. June;39(6):340-4.

[4]Basit A.W., Podczeck F., Newton J.M., Waddington, W.A., Ell, P.J., Lacey, L.F. (2002) Influence of Polyethylene Glycol 400 on the Gastrointestinal Absorption of Ranitidine. Pharm Res. Sept; 19(9):1368-74.

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/s/

MADISA B MACON
08/24/2021 07:56:20 AM

TERRY J MILLER
08/24/2021 09:49:22 AM

NDA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2)
Application Number	213895
Priority or Standard	Priority
Submit Date	September 20, 2019
Received Date	September 20, 2019
PDUFA Goal Date	March 20, 2020
Division	Division of Anti-Infectives
Review Completion Date	March 10, 2020
Established/Proper Name	Vancomycin hydrochloride
(Proposed) Trade Name	Vancomycin Injection
Pharmacologic Class	Glycopeptide antibacterial
Code name	N/A
Applicant	Xellia Pharmaceuticals, ApS
Dosage form/Strength	Injectable (injection solution)/ 5 g/100 mL (50 mg/mL)
Applicant Proposed Dosing Regimen	For Intravenous Use: Adult Patients: 2 g divided either as 0.5 grams every 6 hours or 1 g every 12 hours Pediatric Patients (1 month and older): 10 mg/kg per dose given every 6 hours For Oral Use: Adult Patients: 500 mg to 2 g given in 3 or 4 divided doses Pediatric Patients: 40 mg/kg of body weight in 3 or 4 divided doses. The total daily dosage should not exceed 2 grams.
Applicant Proposed Indication(s)/Population(s)	Treatment of adult and pediatric patients with: 1) Septicemia 2) Infective Endocarditis 3) Skin and Skin Structure infections 4) Bone infections 5) Lower Respiratory Tract infections 6) *Clostridioides difficile*-associated diarrhea (for oral administration only) 7) Enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) (for oral administration only)
Regulatory Action	Complete Response

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	C. Lamont Smith, PharmD
Nonclinical Reviewer	Madisa Macon, PhD, MPH
Nonclinical Team Leader	Terry Miller, PhD
Office of Clinical Pharmacology Reviewer(s)	Anthony Nicasio, PharmD
Office of Clinical Pharmacology Team Leader(s)	Seong Jang, PhD
Clinical Microbiology Reviewer	Kalavati Suvarna, PhD
Clinical Microbiology Team Leader	Avery Goodwin, PhD
Clinical Reviewer	Alma Davidson, MD
Clinical Team Leader	Peter Kim, MD, MS
Cross-Disciplinary Team Leader	Erika Englund, PhD
Division Director (DAI)	Sumathi Nambiar, MD, MPH

Additional Reviewers of Application

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OPDP	Dave Foss, PharmD
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OSE/DMEPA	Deb Myers, PharmD
OSE/DRISK	Naomi Boston, PharmD

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion

OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Chief, Regulatory Project Management Staff	Carmen DeBellas, Pharm D	ORO/DAI	Sections: 3	Select one: ___ Authored X Approved
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Nonclinical Reviewer	Madisa Macon, MPH, PhD	OID/DPT-ID	Sections: 5	Select one: X Authored ___ Approved
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Product Quality	Erika Englund, PhD, Application Technical Lead	OPQ/DNDPI	Section: 1, 4.2	**Select one:** X Authored X Approved
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Clinical Microbiology Team Leader	Avery Goodwin, PhD	OID/DAI	Section: 4.3	**Select one:** ___ Authored X Approved
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Clinical Reviewer	Alma Davidson, MD	OID/DAI	Sections: 1, 2, 4, 7-12, 14	**Select one:** X Authored ___ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Associate Director for Labeling (DAI)	Abimbola Adebowale, PhD	OID/DAI	Sections: 10	**Select one:** ___ Authored X Approved
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Division Director (Clinical)	Sumathi Nambiar, MD, MPH	OID/DAI		**Select one:** ___ Authored X Approved
	Signature: *{See electronic signature page in DARRTS}*			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information

PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

On September 20, 2019, Xellia Pharmaceuticals ApS submitted NDA 213895 Vancomycin Injection, 5 g/100 mL under section 505(b)(2) of the Food Drug and Cosmetic Act (FDCA). The listed drug (LD) is Vancocin® Hydrochloride (Vancomycin Hydrochloride for Injection, USP), approved under ANDA 060180. Of note, it is currently discontinued. A scientific bridge has been established between the proposed product and ANDA 062663, the current Reference Standard (RS) for the in vitro bridging. The Applicant has also provided a letter of cross-reference to their approved drug product, Vancomycin Injection USP, 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL, NDA 211962. The product has been granted Fast Track and Qualified Infectious Disease Product designations.

No new clinical or nonclinical studies were conducted to support this application. However, Xellia had conducted nonclinical studies to assess the toxicity of the excipients N-acetyl-D-alanine (NADA) and polyethylene glycol 400 (PEG 400) to support NDA 211962. Xellia has provided right-of-reference to NDA 211962. 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.

From an OPQ/CMC perspective, this NDA, as amended, has not provided adequate information to assure the identity, strength, purity, and quality of the proposed drug product. Specifically, the Applicant has not provided adequate information on leachables in the drug product. Since the results of the drug product leachables study have not been submitted to the NDA, the safety of any potential leachables cannot be established. Therefore, this NDA is recommended for a complete response by the OPQ and nonclinical teams.

1.1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In NDA 213895, the Applicant is seeking approval of Vancomycin Injection 5 g/100 mL under section 505(b)(2) of the FDCA. The Listed Drug (LD) is Vancocin® Hydrochloride (Vancomycin Hydrochloride for Injection, USP), approved under ANDA 060180, (lyophilized product from Ani Pharmaceuticals). Additionally, since Ani Pharmaceutical's product is discontinued, Vancomycin Hydrochloride for Injection, USP, ANDA 062663 (lyophilized product from Fresenius Kabi) has been used as a Reference Standard for all bridging studies. The Applicant has also provided a letter of cross-reference to their approved drug product, Vancomycin Injection USP, 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL, NDA 211962.

Vancomycin is a tricyclic glycopeptide antibacterial drug. The bactericidal action of vancomycin results primarily from inhibition of cell wall biosynthesis. In addition, vancomycin alters bacterial cell membrane permeability and RNA synthesis.

The Applicant's proposed indications for this product include, for intravenous administration: Septicemia, Infective Endocarditis, Skin and Skin Structure infections, Bone infections, and Lower Respiratory Tract infections; and, for oral administration: *Clostridioides difficile*-associated diarrhea, and Enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains).

The most common adverse reactions associated with administration of vancomycin intravenously are anaphylaxis, "red man syndrome" (or infusion-related reactions), acute kidney injury, hearing loss, and neutropenia. As with NDA 211962, this Vancomycin Injection contains the following excipients: NADA, L-lysine hydrochloride (L-Lys), PEG 400, hydrochloric acid, sodium hydroxide and water. Reproduction studies conducted under NDA 211962 in rabbits with intravenous doses of PEG 400 at approximately 9 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 18 to 20 times the maximum daily human dose, respectively, based on body surface comparisons resulted in maternal toxicity and fetal spinal and cardiovascular malformations in rabbits, and maternal toxicity with no significant adverse embryo-fetal effects in rats. Vancomycin alone did not show adverse developmental effects when administered intravenously to pregnant rats and rabbits during organogenesis at doses less than or equal to the recommended maximum human dose based on body surface area.

To mitigate these risks, the labeling will include a Boxed Warning that this formulation of vancomycin is not recommended for use during pregnancy because it contains the excipients PEG 400 and NADA, which caused fetal malformations in animal reproduction studies. If use of

vancomycin is needed during pregnancy, use of other available formulations of vancomycin is recommended. This information will also be included as a Warning and described in section 8.1.

In the NDA, the Applicant has not submitted the results of the drug product leachables study, therefore, the safety of any potential leachabes in this vancomycin product cannot be established.

A complete response action will be taken based on the OPQ and nonclinical assessments of the submitted information.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CDC reports that in the U.S. methicillin-resistant *S. aureus* (MRSA) infections cause >11,000 deaths annually. While the incidence of invasive MRSA infections appears to be decreasing in U.S. hospitals, the rate of community-associated MRSA infections seems to remain constant. • Severe and fulminant *Clostridioides difficile* infection (CDI) is an increasingly common disease with significant associated morbidity and mortality. Estimated attributable mortality rates range between 30% and 60%.	• Infections due to MRSA and other Gram-positive pathogens can be serious and life-threatening.
Current Treatment Options	• Other approved antibacterial drugs with activity against Gram-positive pathogens including MRSA are linezolid, daptomycin, ceftaroline, telavancin, tigecycline, oritavancin, tedizolid, and dalbavancin. • As per the 2017 IDSA/SHEA guidelines, standard of care treatment for severe and fulminant CDI includes oral vancomycin and intravenous metronidazole.	• Unlike other vancomycin drug products currently on the market which are either lyophilized or frozen pre-mixed products, this product is supplied as a pharmacy bulk package bottle containing 5 g vancomycin in 100 mL equivalent to 50 mg/mL which will require further dilution prior intravenous injection and oral administration.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Vancomycin is commonly used for the treatment of serious MRSA infections and for the treatment of methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins. •Vancomycin for oral use is recommended for the treatment of CDI and staphylococcal enterocolitis caused by both methicillin-susceptible and methicillin-resistant staphylococcal isolates.	• The proposed vancomycin product is a solution which can be used for both intravenous and oral administration.
Risk and Risk Management	• Common adverse reactions with vancomycin include anaphylaxis, "red man syndrome" (or infusion-related reactions), acute kidney injury, hearing loss, and neutropenia. • The excipients PEG 400 and NADA contained in this formulation were found to have potential risks for embryo-fetal toxicity. In nonclinical studies with PEG 400 and NADA, teratogenic findings observed in rabbits and rats, resulted in embryo-fetal findings including spinal malformations and ventricular septal defects.	• This vancomycin product has the potential to cause embryo-fetal toxicity due to the PEG 400 and NADA excipients. • The prescribing information for this product will include a Boxed Warning that this formulation of vancomycin injection is not recommended for use during pregnancy because it contains the excipients PEG 400 and NADA, which caused fetal malformations in animal reproduction studies. If use of vancomycin is needed during pregnancy, use of other available formulations of vancomycin are recommended. This information will also be included as a Warning and described in section 8.1.

1.2. Patient Experience Data

Not applicable.

2 Therapeutic Context

2.1. Analysis of Condition

Staphylococcus aureus is a leading cause of community-acquired and hospital-acquired bacteremia. Patients with *S. aureus* bacteremia can develop a broad array of complications, including osteomyelitis, endocarditis, and sepsis that may be difficult to recognize initially and can increase morbidity. Mortality rates of 20 to 40 percent have been described. Mortality appears to be higher with MRSA compared with methicillin-susceptible *S. aureus* (MSSA) bacteremia.

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality worldwide. Methicillin-resistant *S. aureus* (MRSA) is an uncommon cause of CAP. The strongest risk factors for MRSA pneumonia include known MRSA colonization or prior MRSA infection, particularly involving the respiratory tract.

Acute bacterial skin and skin structure infections (ABSSSI) include cellulitis/erysipelas, wound infection, and major cutaneous abscess. The prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has increased in the past decade, and CA-MRSA is now a predominant cause of purulent ABSSSI in the United States.

Between 2000 and 2011, the incidence of infective endocarditis (IE) in the United States increased from 11 per 100,000 population to 15 per 100,000 population. The three most common causes of infective endocarditis worldwide are staphylococci, streptococci, and enterococci.

Osteomyelitis may be classified based on the mechanism of infection (hematogenous versus non-hematogenous) and the duration of illness (acute versus chronic). Antibacterial therapy is tailored to culture and susceptibility findings when available.

Clostridioides (formerly *Clostridium*) *difficile* remains the most important cause of healthcare-associated diarrhea and has become the most commonly identified cause of healthcare-associated infection in adults in the United States.

Staphylococcus aureus has also been described as a cause of antibiotic-associated enterocolitis (AAE) and diarrhea and is likely an underrecognized etiology. Similar to *C. difficile* infection, risk factors for development of MRSA AAE include advanced age, immunosuppression, prolonged hospital stays, and previous antibacterial drug treatment. Similar to the pathogenesis of *C. difficile*, MRSA enterocolitis is likely caused by a toxin-mediated mechanism.

2.2. Analysis of Current Treatment Options

Current treatment options for MRSA/MSSA infections, as well as, *C. dfficile* infection are listed in the following table. Orally administered vancomycin is the only current treatment approved for staphylococcal enterocolitis.

Table 1: Summary of Treatment Relevant to MRSA/MSSA Infections and *Clostridioides difficile*

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues	Other Comments
Linezolid	• Nosocomial pneumonia • Community-acquired pneumonia including concurrent bacteremia •Complicated skin and skin structure infections	2000	Adults and Adolescents (12 years and older) 600 mg IV or oral every 12 hours Pediatric Patients (birth through 11 years of age): 10 mg/kg IV or oral every 8 hours	Most common adverse reactions (>5% of adult and pediatric patients treated with linezolid) include diarrhea, vomiting, headache, nausea and anemia.	Use in adults and pediatric patients (Birth through 11 years old)
Daptomycin	• Complicated skin and skin structure infections (cSSSI) • Staphylococcal aureus bloodstream infections (bacteremia) in adult patients including those with right-sided infective endocarditis • Staphylococcal aureus bloodstream infections (bacteremia) in pediatric patients (1 to 17 years of age)	2003	cSSSI: Adults: 4 mg/kg IV evry 24 hours Pediatrics: (1 to 17 years) based on Age: -12 to 17 years: 5 mg/kg once every 24 hours -7 to 11 years: 7 mg/kg once every 24 hours -2 to 6 years: 9 mg/kg once every 24 hours - 1 to less than 2 years: 10 mg/kg once every 24 hours *Staph aureus* bacteremia including those with right-sided IE: Adults: 6 mg/kg IV once every 24 hours *Staph aureus* bacteremia: Pediatrics (1 to 17 years) based on age: -12 to 17 years: 7 mg/kg once every 24 hours -7 to 11 years: 9 mg/kg once every 24 hours -1 to 6 years: 12 mg/kg once every 24 hours	Adult cSSSI Patients: Most common ARs that occurred in ≥2% were diarrhea, headache, dizziness, rash, abnormal LFTs, elevated CPK, urinary tract infections, hypotension, and dyspnea. Pediatric cSSSI Patients: Most common ARs that occurred in ≥2% were diarrhea, vomiting, abdominal pain, pruritus, pyrexia, elevated CPK, and headache. Adult *S. aureus* bacteremia/endocarditis Patients: Most common ARs that occurred in ≥5% were sepsis, bacteremia, abdominal pain, chest pain, edema, pharyngolaryngeal pain, pruritus, increased sweating, insomnia, elevated CPK, and hypertension. Pediatric *S. aureus* bacteremia Patients: Most common ARs that occurred in ≥5% were vomiting and elevated CPK.	Use in adults and pediatric patients (1 to 17 years of age)

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability	Other Comments
Tigecycline	• Complicated skin and skin structure infections •Complicated Intra-abdominal Infections	2005	Adults: Initial dose of 100 mg followed by 50 mg every 21 hours IV	Most common adverse reactions (>5%) are nausea, vomiting, diarrhea, abdominal pain, headache, and increased SGPT.	Use in adult patients only.
Telavancin	• Complicated skin and skin structure infections •Hospital-acquired and Ventilator-aspociated bacterial pneumonia	2009	Adults: cSSSI: 10 mg/kg IV every 24 hours. Dosage adjustment in patients with renal impairment. HABP/VABP: 10 mg/kg IV evry 24 hours. Dosage adjustment in patients with renal impairment.	Most common adverse reaction (>10%) in HABP/VABP is diarrhea. In cSSSI trials, most common adverse reactions (>10%) in HABP/VABP are taste disturbance, nausea, vomiting, and foamy urine.	Use in adult patients only.
Ceftaroline	•Acute Bacterial Skin and Skin Structure Infections (MRSA and MSSA)	2010	Adults: 600 mg IV every 12 hours Pediatrics: •2 months to less than 2 years: 8 mg/kg evry 8 hours • greater than or equal to 2 years to less than 18 years (≤33 kg): 12 mg/kg every 8 hours	Most common adverse reactions (Ars) occurring in >2% of adult patients and ≥3% of pediatric patients are diarrhea, nausea, and rash. Additional ARs that occurred in ≥3% of pediatric patients include vomiting and pyrexia.	Use in adult and pediatric patients (2 months to less than 2 years; 2 years to less than 18 years)
Tedizolid	•Acute Bacterial Skin and Skin Structure Infections (MRSA and MSSA)	2014	Adults: 200 mg IV/oral once daily	Most common adverse reactions(≥2%) are nausea, headache, diarrhea, infusion-or injection-related adverse reactions, vomiting, and dizziness.	Use in adult patients only.
Oritavancin	•Acute Bacterial Skin and Skin Structure Infections (MRSA and MSSA)	2014	Adults: 1200 mg IV single dose over 3 hours	Most common adverse reactions (≥3%) include headache, nausea, vomiting, limb and subcutaneous abscesses, and diarrhea.	Use in adult patients only.

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues	Other Comments
Dalbavancin	•Acute Bacterial Skin and Skin Structure Infections (MRSA and MSSA)	2014	Adults: Estimated CrCL ≥30 mL/min or on regular hemodialysis: **Single Dose Regimen** 1500 mg **Two-Dose Regimen** 1000 mg followed one week later by 500 mg < 30 mL/min and not on regular hemodialysis: **Single Dose Regimen** 1125 mg **Two-Dose Regimen** 750 mg followed one week later by 375	Most common adverse reactions were nausea (4.7%), headache (3.8%), and diarrhea (3.4%).	Use in adult patients only.
Omadacycline	Acute Bacterial Skin and Skin Structure Infections (MRSA and MSSA)	2018	Adults: Day 1: 200 mg by intravenous infusion over 60 minutes OR 100 mg by intravenous infusion over 30 minutes twice OR 100 mg by intravenous infusion over 30 minutes once daily OR 300 mg orally once daily	Most common adverse reactions (≥2%) are nausea, vomiting, infusion site reactions, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, hypertension, headache, diarrhea, insomnia, and constipation.	Use in adult patients only.
Antibacterial Agent Approved For *C. Difficile* Associated Diarrhea					
Fidaxomicin	*Clostridium difficile*-Associated Diarrhea (CDAD)	2011	Adults: One 200 mg tablet orally twice daily for 10 days with or without food	Most common adverse reactions (incidence ≥ 2 %) are nausea, vomiting, abdominal pain, gastrointestinal hemorrhage, anemia, and neutropenia.	Use in adult patients only.
Alternative (Off-label Use) Antibacterial Agent For *C. Difficile* Associated Diarrhea					

Metronidazole	Intra-abdominal infections caused by Clostridial species	1980	Adults: The recommended dosage schedule for adults: Loading dose:15 mg/kg infused IV over 1 hour (approximately 1 g for a 70 kg).Maintenance Dose 7.5 mg/kg infused over 1 hour every 6 hours (approximately 500 mg for a 70 kg adult). The first maintenance dose should be instituted 6 hours following the initiation of the loading dose.	Most common adverse reactions are gastrointestinal signs and symptoms including nausea, diarrhea, abdominal pain, and vomiting.	Use in adult patients.

Reviewer's Comment: The list of antibacterial drugs noted in the table above is not all inclusive. Clinical data regarding use of older antibacterial drugs that show in vitro activity against S. aureus and MRSA, such as trimethoprim-sulfamethoxazole, clindamycin, tetracyclines, and to some extent, quinopristin-dalfopristin are not included here. The M.O. also notes that Firvanq, a vancomycin oral solution for the treatment of C. difficile-associated diarrhea and staphylococcal enterocolitis, was recently approved.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant was granted QIDP for this drug product under IND 129733 and has been granted Fast Track designation during this review cycle. Both the QIDP and Fast Track designations apply to the following indications:

1) Septicemia
2) Infective Endocarditis
3) Skin and Skin Structure infections
4) Bone infections
5) Lower Respiratory Tract infections
6) *Clostridioides difficile*-associated diarrhea (for oral administration only)
7) Enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains), (for oral administration only)

3.2. Summary of Presubmission/Submission Regulatory Activity

A Type B Pre-IND meeting request was submitted to the Agency on January 20, 2016. The Agency provided written responses on April 15, 2016. A Pre-NDA meeting request was submitted to the Agency on May 10, 2019. The Agency provided written responses on July 09, 2019.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No clinical trials were conducted by the Applicant; therefore, no inspections were performed by OSI.

4.2. Product Quality

Novel Excipients: No
Any Impurity of Concern: No. The impurity [redacted] (b) (4) was adequately qualified for safety with nonclinical studies. See Section 5.5.

Table 2. Quantitative composition, functions of components, and references to standards for Xellia Vancomycin Injection, 5 g/100 mL

Name of Ingredient	Quantity per unit (mg/vial)	% (w/w)	Function	Reference to Standard
Vancomycin[1]	5,000	4.76	(b) (4)	In house
N-Acetyl-D-Alanine	4,524	4.30		In house
L-Lysine Hydrochloride (Monochloride)	1,260.3	1.2		USP
Polyethylene glycol 400	11,300	10.8		NF
Sodium hydroxide[2]	q.s.	q.s.	pH adjusting agent	NF
Water for Injection	q.s. 100.0 mL	q.s.	(b) (4)	USP
[redacted] (b) (4)				
TOTAL MASS[4]	**105,100.0 mg**	**100.0 %**	**NA**	

NA – Not Applicable
[1]An overfill of (b) (4) % is employed for the manufacture of Vancomycin Injection, 5 g/100 mL, to ensure administration of the labelled amount of active (please refer to Section 3.2.P.2 Pharmaceutical Development)
[2]Used during (b) (4) for pH adjustment within the range of (b) (4)
[redacted] (b) (4)
[4]Equivalent to 100.0 mL of injection solution, respectively, calculated based on a density of 1.051 g/mL

Xellia Vancomycin Injection is a solution that contains the excipients polyethylene glycol 400 (PEG 400), N-acetyl-D-alanine (NADA), L-lysine, sodium hydroxide, [redacted] (b) (4)

In the drug product solution, [redacted] (b) (4) was identified as a novel degradation impurity. The impurity was adequately qualified for general toxicity and genotoxicity from a Pharmacology/Toxicology perspective. See Section 5.5 Nonclinical Pharmacology/Toxicology.

This NDA, as amended, has not provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for a complete response by OPQ at this time. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama on January 2, 2020. The Biopharmaceutics review noted that the proposed product, LD and RS have the same active ingredient, same strength, same 2 routes of administration and the same dosage form at the time of administration; however, these products differ in the excipients (the LD and RS have no excipients). The Applicant provided information/data to demonstrate that the inclusion of the excipients [NADA, l-lysine HCl and PEG 400, besides pH adjusting agent] in the proposed product is not expected to alter the pharmacokinetics or the local effect upon intravenous or oral administration, respectively. The Biopharmaceutics review concluded that the Applicant provided sufficient information to support the bridge between the proposed drug product and the LD/RS for intravenous as well as oral administration. However, the drug product review found the NDA inadequate. Therefore, this NDA is recommended for a complete response from a CMC perspective.

An information request was sent on October 28, 2019 requesting results from a leachables study. The Applicant responded on December 16, 2019 that the leachables study would be submitted at the end of March 2020. However, since the PDUFA date is March 20, 2020, the proposed timeline would not allow sufficient time to review the study prior to the action date. The following information request was sent on December 19, 2019:

> *We acknowledge your December 16, 2019 response that you plan to submit the screening leachables study at the end of March 2020, but we are not able to guarantee that we will be able to review any information received after January 21, 2020 as specified in our Information Request of December 9, 2019. This may be considered an approvability issue for your application.*

The leachables study was not received as of March 9, 2020. Therefore, this NDA is recommended for a Complete Response from a CMC perspective.

4.3. Clinical Microbiology

No new microbiology data were submitted in this NDA.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Xellia Pharmaceuticals ApS conducted two nonclinical studies to bridge their Vancomycin Injection (also referred to as Xellia Vancomycin in this review) to that of the reference standard (RS) Fresenius Kabi USA LLC's Vancomycin Hydrochloride for Injection (ANDA 062663; also referred to as Fresenius Vancomycin in this review) as the Listed Drug (LD) Ani Pharmaceuticals Vancomycin Hydrochloride for Injection (ANDA 060180; also referred to as Ani Vancomycin) has been discontinued. Xellia conducted a 13-week intravenous comparative toxicology and toxicokinetic study in dogs with Fresenius Vancomycin and a degraded formulation of Xellia, a 28-day oral comparative toxicology and toxicokinetic study in dogs with Fresenius Vancomycin and Xellia Vancomycin, and an in vitro human blood compatibility and hemolytic potential study with Xellia Vancomycin. The Applicant also submitted several nonclinical studies to assess the mutagenic potential of the impurity (b) (4) and nonclinical studies and the safety of the excipients N-acetyl-D-alanine (NADA) and polyethylene glycol 400 (PEG 400). The Applicant will rely on the Agency's prior findings of safety and effectiveness for vancomycin, as well as the nonclinical information in labeling of the listed drug, Vancomycin Hydrochloride for Injection (ANDA 060180) to support the current NDA.

Xellia Vancomycin contains the excipients polyethylene glycol 400 (PEG 400), N-acetyl-D-alanine (NADA), L-lysine, sodium hydroxide, (b) (4). Every 5 gram/100 mL vial of Xellia Vancomycin contains 11.3 grams of PEG 400, 4.524 grams of NADA, 1.260 grams of L-lysine, NaOH for pH, (b) (4), and water to volume. There are no novel excipients in Xellia Vancomycin; all excipients in Xellia Vancomycin are at lower daily amounts compared to other FDA approved products.

Based on the overall findings of the submitted nonclinical toxicology studies, Xellia Vancomycin appears comparable in its general toxicity to Fresenius Vancomycin evaluated in repeat dose IV and oral studies in dogs. The toxicokinetic profile of Xellia Vancomycin was also comparable to Fresenius Vancomycin in dogs for IV administration but not oral administration.

Pharmacokinetics

From the 13-week intravenous study in dogs, the systemic exposure of vancomycin in a degraded formulation of Xellia Vancomycin was comparable to that of the RS. The PK of vancomycin on Day 91 in the Xellia Vancomycin group at 75mg/kg was 152-167 mg/mL and 368-372 mcg*hr/mL (C_{max} and AUC $_{0\text{-}Tlast}$) and in Fresenius Kabi Vancomycin group at 75 mg/kg was 164-169 mcg/mL and 394-403 mcg*hr/mL (C_{max} and AUC $_{0\text{-}Tlast}$).

From the 28-day oral study in dogs, the systemic exposure of vancomycin from Xellia Vancomycin was not comparable to that of the RS. The PK of vancomycin on Day 28 in the Xellia

Vancomycin group at 100 mg/kg was 0.63-0.70 mcg/mL and 0.8-1.9 mcg*hr/mL (C_{max} and AUC $_{0\text{-}Tlast}$) and in the Fresenius Kabi Vancomycin group at 100 mg/kg was 1.21-1.46 mcg/mL and 2.8-3.5 mcg*hr/mL (C_{max} and AUC $_{0\text{-}Tlast}$). The plasma concentrations of vancomycin in animals in the Xellia Vancomycin group were 29-54% lower compared to concentrations in the Fresenius Vancomycin group.

No studies were conducted with Xellia Vancomycin Injection to determine the distribution, metabolism, or excretion of this formulation at either route of administration. From a literature review, vancomycin is poorly absorbed following oral administration and thus systemic exposure is low.

Safety Pharmacology

No safety pharmacology studies were conducted by the Applicant. From the labeling of the LD, low blood pressure and bradycardia were noted in studies with dogs administered 25 mg/kg vancomycin at 25 mg/mL and an infusion rate of 13.3 mL/min.

Repeat-Dose Toxicology /Comparative Nonclinical Toxicology

In the 13-week IV study in dogs, the Applicant tested a degraded formulation of Xellia Vancomycin to qualify the general toxicity of the impurity (b) (4)) and to compare the toxicity of their product to the RS. (b) (4) is an impurity found in the drug product. Xellia Vancomycin was degraded for 5 months under accelerated conditions (higher temperatures and humidity) to produce a formulation with (b) (4) For 13 weeks, dogs were dosed with 75 mg/kg/day Xellia Vancomycin (b) (4) 75 mg/kg/day Fresenius Vancomycin, or saline control. Limited toxicity was observed in either Xellia Vancomycin or Fresenius Vancomycin groups. Similar minimal kidney toxicity was noted in Xellia and Fresenius Vancomycin groups compared with Controls. There were slight differences in hemolysis and thrombosis at the injection sites in Xellia Vancomycin animals compared with Fresenius Vancomycin animals. It was concluded that the toxicity of Xellia Vancomycin was equivocal to that of Fresenius Vancomycin and the impurity, (b) (4) was qualified for nonclinical general safety. Systemic vancomycin levels in dogs were approximately 2.4-3.9 fold higher than systemic vancomycin levels in humans at the recommended clinical dose based on mean plasma concentrations.

In the 28-day oral study in dogs, the Applicant compared the toxicity of Xellia Vancomycin to the RS Fresenius Vancomycin. For 28 days, Beagle dogs were dosed with 100 mg/kg/day Xellia Vancomycin, 100 mg/kg/day Fresenius Vancomycin, or saline control by gastric intubation. Similar increased incidence of mild vomiting was noted in both Xellia and Fresenius Vancomycin groups and increased frequency of vomiting was noted in Xellia Vancomycin groups when compared with Controls. Slight changes in hematology, clinical chemistry, urinalysis, and organ weights were also noted with Xellia Vancomycin and Fresenius Vancomycin when compared with Controls. The toxicity findings in the Xellia Vancomycin group were considered comparable to that of the Fresenius Vancomycin group. Based on body surface comparisons, the levels of

vancomycin in dogs at 100 mg/kg oral Xellia Vancomycin were approximately 1.6 fold higher than levels of vancomycin in humans at the recommended clinical dose.

Genetic Toxicology and Carcinogenicity

No genetic toxicology studies were conducted with Xellia Vancomycin. From the labeling of the LD, vancomycin was not found to be mutagenic based on standard laboratory tests, which were not described. No carcinogenicity studies have been conducted with vancomycin or Xellia Vancomycin.

The Applicant conducted a QSAR assessment of the impurity, (b) (4) and found that the mutagenicity profile of (b) (4) was similar to that of vancomycin based on their shared structural similarities. Based on this information, (b) (4) was concluded to be a (b) (4) impurity and is qualified for genetic toxicity.

Reproductive Toxicology

No reproductive studies were conducted with Xellia Vancomycin. From the labeling for the LD, vancomycin did not cause changes in fetal body weight or development when administered to pregnant rats or rabbits during organogenesis at 200 mg/kg/day IV or 120 mg/kg/day IV, respectively. When administered during pregnancy, maternal toxicity was observed in rats (following ≥120 mg/kg/day) and rabbits (following ≥80 mg/kg/day).

Embryo-fetal toxicity studies with NADA (rats and rabbits) and PEG 400 (rabbits) were submitted with the application. These studies were reviewed in full as part of the nonclinical review for the referenced NDA 211962 that was approved on 2/15/2019. Summaries and a review of the studies are included below.

Other Toxicology

Xellia's Vancomycin Injection was compatible with human serum and plasma and did not show potential for hemolysis. The Applicant submitted quantitative structure–activity relationship (QSAR) assays to qualify the impurity, (b) (4) for genetic toxicity in accordance with ICH Guidance M7(R1)[1]. Additional nonclinical studies were submitted to this NDA to qualify the excipients PEG 400 and NADA. PEG 400 and NADA were considered adequately qualified in the referenced NDA 211962. These studies were reviewed in full as part of the nonclinical review for NDA 211962 that was approved on 2/15/2019. Summaries and a review of the studies are included below.

RECOMMENDATION

[1] ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m7r1-assessment-and-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit-potential

The Applicant has provided sufficient nonclinical safety information for Xellia Vancomycin based on the IV and oral bridging studies to the RS Fresenius Kabi Vancomycin. The impurity, (b) (4) was qualified for general and genetic toxicity based on submitted nonclinical studies. However, this NDA cannot be recommended for approval without complete information regarding leachables from the container closure of the final drug product. Therefore, due to the absence of a recommended leachable study for this final drug product, a complete response is supported from a Pharmacology/Toxicology perspective. Recommendations for edits to the Pharmacology/Toxicology relevant sections of the labeling were provided to the Applicant.

5.2. Referenced NDAs, BLAs, DMFs

NDA 211962, ANDA 062663 (Reference Standard), ANDA 060180 (Listed Drug), DMF 031868 (drug substance), DMF (b) (4)

5.3. Pharmacology

ADME/PK

Nonclinical studies were conducted to compare the toxicokinetic (TK) parameters of Xellia's Vancomycin Injection to that of the reference standard Fresenius Kabi Vancomycin. The TK of vancomycin from the 13-week intravenous and 28-day oral comparative toxicology study in Beagle Dogs are included in the tables below.

Table 3. Intravenous Pharmacokinetics

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>TK data from comparative toxicology studies
A 13-Week Intravenous Infusion Vancomycin Impurity Qualification Study, Followed by a 4-Week Recovery Period in Beagle Dogs, Study #62479
• Dogs dosed with 75 mg/kg/day for 13 weeks
• Samples collected on Days 1, 45, and 91 of the treatment period
• TK of Vancomycin in Xellia Vancomycin Injection does not appear to be different from Vancomycin TK in the LD Fresenius Vancomycin Injection
• TK data from male and female dogs were combined.</td><td><u>Dog Xellia Vancomycin Injection</u>
T1/2: 1.70 – 1.89 hr
<table>
<tr><th>Day</th><th>Sex</th><th>Tmax (hr)</th><th>Cmax (mcg/mL)</th><th>AUC0-Tlast (mcg*hr/mL)</th></tr>
<tr><td>1</td><td>M</td><td>0.929</td><td>153</td><td>328</td></tr>
<tr><td>1</td><td>F</td><td>1.00</td><td>243</td><td>365</td></tr>
<tr><td>45</td><td>M</td><td>1.00</td><td>169</td><td>344</td></tr>
<tr><td>45</td><td>F</td><td>1.00</td><td>163</td><td>324</td></tr>
<tr><td>91</td><td>M</td><td>0.857</td><td>152</td><td>368</td></tr>
<tr><td>91</td><td>F</td><td>0.929</td><td>167</td><td>372</td></tr>
</table>
Accumulation: None
Sex Related Difference: No

<u>Dog Fresenius Vancomycin Injection</u>
T1/2: 1.61 – 1.82 hr
<table>
<tr><th>Day</th><th>Sex</th><th>Tmax (hr)</th><th>Cmax (mcg/mL)</th><th>AUC0-Tlast (mcg*hr/mL)</th></tr>
<tr><td>1</td><td>M</td><td>0.893</td><td>177</td><td>374</td></tr>
<tr><td>1</td><td>F</td><td>1.04</td><td>191</td><td>358</td></tr>
<tr><td>45</td><td>M</td><td>0.929</td><td>167</td><td>396</td></tr>
<tr><td>45</td><td>F</td><td>1.00</td><td>166</td><td>389</td></tr>
<tr><td>91</td><td>M</td><td>1.04</td><td>164</td><td>403</td></tr>
<tr><td>91</td><td>F</td><td>0.929</td><td>169</td><td>394</td></tr>
</table>
Accumulation: None
Sex Related Difference: No</td></tr>
</table>

Table 4. Oral Pharmacokinetics

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Absorption from comparative toxicology studies
A 28-Day Repeated Dose Oral Toxicity and Toxicokinetics Study of Xellia's Vancomycin in Beagle Dogs Followed By a 14-Day Recovery Period Dogs
• Dogs dosed with 100 mg/kg/day
• Samples collected on Days 1 and 28 of the treatment period</td><td>• Oral absorption of vancomycin was significantly lower in dogs dosed with Xellia Vancomycin compared with dogs dosed with Fresenius Vancomycin.
• Cmax and AUC values for vancomycin were 29-54% lower in dogs dosed with Xellia Vancomycin compared with dogs dosed with Fresenius Vancomycin.</td></tr>
<tr><td>TK data from comparative toxicology studies
A 28-Day Repeated Dose Oral Toxicity and Toxicokinetics Study of Xellia's Vancomycin in Beagle Dogs Followed By a 14-Day Recovery Period Dogs
• Dogs dosed with 100 mg/kg/day
• Samples collected on Days 1 and 28 of the treatment period</td><td><u>Dog Xellia Vancomycin Injection</u>
<table>
<tr><th>Day</th><th>Sex</th><th>Tmax (hr)</th><th>Cmax (mcg/mL)</th><th>AUC0-Tlast (mcg*hr/mL)</th></tr>
<tr><td>1</td><td>M</td><td>1.4</td><td>0.70**</td><td>1.3**</td></tr>
<tr><td>1</td><td>F</td><td>1.0</td><td>0.94</td><td>1.9**</td></tr>
<tr><td>28</td><td>M</td><td>1.1</td><td>0.70**</td><td>1.9</td></tr>
<tr><td>28</td><td>F</td><td>1.0**</td><td>0.63</td><td>0.8*,**</td></tr>
</table>
Accumulation: None
Sex Related Difference: No

<u>Dog Fresenius Vancomycin Injection</u>
<table>
<tr><th>Day</th><th>Sex</th><th>Tmax (hr)</th><th>Cmax (mcg/mL)</th><th>AUC0-Tlast (mcg*hr/mL)</th></tr>
<tr><td>1</td><td>M</td><td>0.8</td><td>1.58</td><td>4.0</td></tr>
<tr><td>1</td><td>F†</td><td>1.5</td><td>1.83</td><td>4.3</td></tr>
<tr><td>28</td><td>M</td><td>0.9</td><td>1.46</td><td>3.5</td></tr>
<tr><td>28</td><td>F†</td><td>0.6*</td><td>1.21</td><td>2.8</td></tr>
</table>
Accumulation: None
Sex Related Difference: No
Values with "*" on Day 28 are significantly different from Day 1, p<0.05 Student's t-test.
Values with "**" are significantly different from FK Vancomycin, p<0.05 Student's t-test.</td></tr>
</table>

Reviewer's Comments: There was no difference in PK between the reference drug and Xellia Vancomycin from intravenous injection. Vancomycin systemic exposures (Cmax and AUC) from oral administration of Xellia Vancomycin Injection were lower when compared to Fresenius vancomycin. In their application, Xellia argued that lower systemic exposures would not lower the efficacy for the oral indications as systemic exposures are not needed for the clinical indication. †However, in the 28-day study, one female dog in the Xellia Vancomycin group was omitted from the mean group statistics on Day 1 and 28 as the plasma levels for that dog were 49-138 fold higher than other animals in that group on Day 1. This animal was noted to have vomited 5 minutes post-dosing on Day 1. The Investigators suspected that the high vancomycin plasma levels were due to partial tracheal dosing or aspiration of Xellia Vancomycin. Samples from this animal were not taken on Day 28. If true, it is possible that vomiting may impact the efficacy of Xellia Vancomycin when administered orally. In addition, it is likely that inclusion of those values would have altered the mean PK values for Xellia Vancomycin in females on Day 1.

Since the Investigators did not take samples from that dog on Day 28, it is unclear if vancomycin plasma levels would have remained elevated compared to others in the group.

5.4. Toxicology

5.4.1. Comparative Toxicology

A 13-Week Intravenous Infusion Vancomycin Impurity Qualification Study, Followed by a 4-Week Recovery Period in Beagle Dogs, Study #62479

- Minimal toxicity was noted for dogs dosed with Xellia Vancomycin or Fresenius Vancomycin at 75 mg/kg/day vancomycin. Mild kidney toxicity was noted in both Xellia and Fresenius Vancomycin groups compared to Controls. There were slight differences in hemolysis and thrombosis at injection sites in Xellia Vancomycin groups compared to Fresenius Vancomycin.
- The toxicokinetic values for vancomycin did not appear different in animals dosed with Xellia Vancomycin compared with the reference standard Fresenius Vancomycin.
- The presence of the impurity, (b) (4) did not appear to affect the toxicity of Xellia Vancomycin. (b) (4) is qualified for general toxicity at the clinical dose; (b) (4) mg/kg (b) (4) in dogs corresponds to a human equivalent dose (HED) of (b) (4) mg (b) (4) at the maximum recommended human dose of 2 grams vancomycin. The Applicant requested a (b) (4)% specification for (b) (4) in the drug product which would result in (b) (4) mg of (b) (4) at the maximum recommended human dose of 2 grams vancomycin.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	75 mg/kg/day for 13 weeks
Route of administration:	Intravenous Injection (1-hour infusion) from a surgically implanted indwelling catheter in the cephalic or saphenous vein
Formulation/Vehicle:	Xellia Vancomycin Injection (degraded for 5 months) Fresenius Vancomycin Hydrochloride for injection 0.9% Sodium Chloride (NaCl)
Species/Strain:	Beagle Dog (b) (4)
Number/Sex/Group:	5 animals/sex/group
Age:	8 to 10 months old

Satellite groups/ unique design:	Recovery period 2 animals/sex/group; 4 week recovery period
Deviation from study protocol affecting interpretation of results:	None

Table 5: Observations and Results: Changes from Control (Study #62479-Dog)

Parameters	Major findings
Mortality	None
Clinical Signs	Unremarkable*
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	Unremarkable
Clinical Chemistry	Unremarkable
Urinalysis	Unremarkable
Gross Pathology	XV: Dark areas and gelatinous material at infusion site consistent with increased thrombosis. Effects resolved following the recovery period.
Organ Weights	Unremarkable
Histopathology Adequate battery: **Yes**	FV: At infusion site minimal thrombus. Microscopic changes of mild kidney toxicity. All effects resolved following the recovery period. XV: At infusion site minimal to moderate perivascular hemorrhage, minimal to mild acute perivascular inflammation, mild thrombus. Microscopic changes of mild kidney toxicity. All effects resolved following the recovery period.

Control= Saline Control; FV= Fresenius Kabi Vancomycin; XV= Xellia Vancomycin

*Reviewer's Comments: *In Study 62479, the investigators noted in the results section that one male animal in the Xellia Vancomycin group was noted with "signs of possible convulsion and/or seizures on Days 40 and 41, prior to dosing administration." However, there is no indication of these observations in the individual detailed clinical observations in Appendix 9. This animal was only noted to have loose feces. Vancomycin administration can lead to seizures, albeit rarely. It is not clear whether the excipients and/or impurities in Xellia Vancomycin potentiated this effect in that animal.*

It is the opinion of this reviewer that the Applicant did not dose the FV or XV animals with enough vancomycin to elicits signs of overt toxicity. Therefore, it was difficult to determine whether there were toxicological differences between the two formulations compared with controls. However, under the conditions tested the toxicity of Xellia Vancomycin appears to be similar to that of the RS Fresenius Vancomycin. The 75 mg/kg dose of vancomycin in dogs corresponds to a HED of approximately 40.6 mg/kg. Although there was no NOAEL for this study as the Applicant only tested one dose, the 75 mg/kg dose in dog would result in a safety factor of more than 2.5 fold above a 1-gram dose of vancomycin in humans based on systemic exposures. In addition, the impurity, (b) (4) did not appear to affect the toxicity profile of Xellia Vancomycin. The (b) (4) mg/kg of (b) (4) in dogs corresponds to a human equivalent dose of (b) (4) mg/kg or (b) (4) mg (b) (4) at the maximum recommended human dose of 2 grams

vancomycin. The Applicant requested a (b) (4)% specification for (b) (4) in the drug product which would result in (b) (4) mg of (b) (4) at the maximum recommended human dose of 2 grams vancomycin. Therefore, this study qualifies the general toxicological safety of (b) (4) at (b) (4)% of the drug product Xellia Vancomycin.

A 28-Day Repeated Dose Oral Toxicity and Toxicokinetics Study of Xellia's Vancomycin in Beagle Dogs Followed By a 14-Day Recovery Period, Study #344368

- Slight toxicity was observed following oral exposures to Xellia Vancomycin and Fresenius Vancomycin when compared with Controls. Mild vomiting and mild differences in hematology, clinical chemistry, and urinalysis measurements were noted for both Xellia Vancomycin and Fresenius Vancomycin groups compared with Controls. Fresenius Vancomycin reduced thymus weights compared with Controls; Xellia Vancomycin increased adrenal weights compared with Controls.
- The toxicity of oral Xellia Vancomycin was considered equivocal to that of oral Fresenius Vancomycin when compared to Controls.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	100 mg/kg/day for 28 days
Route of administration:	Oral administration by gastric intubation
Formulation/Vehicle:	Xellia Vancomycin Injection Fresenius Vancomycin Hydrochloride for Injection 0.9% Sodium Chloride (NaCl)
Species/Strain:	Beagle Dog (b) (4)
Number/Sex/Group:	3 animals/sex/group
Age:	6 to 7 months
Satellite groups/ unique design:	Recovery animals (2 animals/sex/group); 14-day recovery period
Deviation from study protocol affecting interpretation of results:	None

Table 6: Observations and Results: Changes from Control (Study #344368-Dog)

Parameters	Major findings
Mortality	None
Clinical Signs	FV: Mild vomiting (increased incidence) XV: Mild vomiting (increased incidence and frequency)
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable

ECG	Unremarkable
Hematology	FV: Decreased reticulocytes and % reticulocytes in males (-39.9%, -37%) XV: Increased % neutrophils in females (+6.5%)
Clinical Chemistry	XV: Increased phosphorus in males (+14.0%); increased triglycerides in males (+33.3%); increased albumin/globulin in females (+13.3%)
Urinalysis	Unremarkable FV: increased bilirubin in females; increased specific gravity in females XV: increased pH in males; increased bilirubin in females; increased specific gravity in females
Gross Pathology	Unremarkable
Organ Weights	XV: Thymus weights were decreased compared to FV weights (-40.7% absolute; -38.9% relative); Adrenal glands increased in XV females (47.0%) compared to controls
Histopathology Adequate battery: **Yes**	No treatment related effects

Control= Saline Control; FV= Fresenius Kabi Vancomycin; XV= Xellia Vancomycin

Reviewer's Comments: The Investigators excluded one animal from Xellia Vancomycin group from the grouped TK analysis due to higher systemic levels (49-138 fold higher) when compared with other animals in that group on Day 28. That animal was also noted with vomiting 5 minutes post-dosing of Day 1. The Investigators suspected that the high vancomycin plasma levels were due to partial tracheal dosing or aspiration of Xellia Vancomycin. Samples from this animal were not taken on Day 28. If the elevated vancomycin plasma levels were due to aspiration of Xellia Vancomycin, it is also possible that vomiting may impact the local efficacy of Xellia Vancomycin when administered orally. In addition, it is likely that inclusion of those values would have impacted the mean PK values for Xellia Vancomycin in females on Day 1. Since the Investigators did not take samples from that dog on Day 28, it is unclear if vancomycin plasma levels would have remained elevated compared to others in the group.

Based on the findings from this study, the nonclinical safety of oral Xellia Vancomycin is adequate as there were no major differences in toxicity observed in dogs dosed with 100 mg/kg Xellia Vancomycin or 100 mg/kg Fresenius Vancomycin when compared with Controls. A 100 mg/kg dose in dogs corresponds to 54.1 mg/kg HED (approximately 1.62 fold higher than the clinical dose of 33.3 mg/kg in a 60 kg human).

General toxicology; additional studies
Hemolytic Potential of Xellia Vancomycin

Hemocompatibility Test (Hemolysis and Flocculation) of Xellia Vancomycin Formulation Prepared with 5% Dextrose and 0.9% NaCl, in Human Blood, #351660

The compatibility and hemolytic potential of Xellia Vancomycin Injection was investigated at 6.3, 63, and 315 mcg/mL concentrations with human whole blood, plasma, and serum. 2.0% saponin and 0.9% NaCl were used as positive and vehicle controls, respectively. There was no

precipitation or coagulation observed in human serum or plasma samples incubated with Xellia Vancomycin Injection. The hemolytic potential of Xellia Vancomycin was 1.07%, 0.96%, and 0.99%, and similar to the that of the vehicle control at 0.81% and 0.86%. Thus, hemolysis was not observed in the whole blood incubated with Xellia Vancomycin Injection. It was concluded that Xellia Vancomycin Injection is compatible with human serum and plasma and that it does not cause hemolysis under the conditions of the study. This study was conducted under GLP regulations.

5.4.2. Genetic Toxicology

No genetic toxicology studies were conducted for NDA 213895. The Applicant submitted several QSAR assays to assess the mutagenic potential of the impurity (b) (4) For a summary of the studies and their findings see Section 5.5.5 Other Toxicology Studies below.

5.4.3. Carcinogenicity

No carcinogenicity studies were conducted for NDA 213895.

5.4.4. Reproductive and Developmental Toxicology

No studies were conducted with Xellia Vancomycin to assess its potential reproductive or developmental toxicity. The Applicant submitted embryo-fetal development studies for two of the excipients NADA and PEG 400 in Xellia Vancomycin. These studies were reviewed in full and found adequate by Dr. Madisa Macon in Section 5 of the Unireview for the referenced NDA 211962. For summaries of those reviews, see Section 5.5.5 Other Toxicology Studies below.

5.4.5. Other Toxicology Studies

Mutagenicity Assessment of Impurity (b) (4)

The novel impurity (b) (4) was assessed for its mutagenic potential in accordance with ICH Guidance M7(R1). The Applicant submitted two QSAR prediction models to assess the genotoxic potential of (b) (4) Derek Nexus 6.0.1 (expert rule-based) and Leadscope Model Applier v2.4.1-36 (statistical-based). In the Derek Nexus Report (Nexus 2.2.2, Derek KB 2018 1.1), the model predicted a plausible alert for in vitro mammalian chromosome damage, mutagenicity, and non-specific genotoxicity. The model was negative for mutagenicity in bacteria. Collectively, the mutagenic potential of (b) (4) was determined to be equivocal under the conditions of the model. In the Leadscope Model Applier Report (Applier 2.4.5-7, Enterprise 3.7.5-7, Personal 4.7.5-7), the model predictions for in vitro and in vivo mutagenicity and clastogenicity were negative or "Not in Domain". Based on chemical structure, the model

predicted (b) (4) to be negative for *in vitro* microbial assays, *in vivo* mouse micronucleus, and mammalian *in vivo* rodent assays. Seven of the 13 computational models were "Not in Domain", as the model was unable to calculate a prediction. Due to chemical structural similarities between (b) (4) and vancomycin, the Applicant calculated QSAR predications for vancomycin using the same models (Derek and Leadscope). The results of vancomycin were the same under the conditions of both models. From the labeling of the LD Ani Vancomycin, vancomycin was not found to be mutagenic based on standard laboratory tests. Impurities that share structural alerts with an API are classified as (b) (4) and considered non-mutagenic per ICH M7(R1). Therefore, (b) (4) was predicted to be negative for mutagenicity and has been adequately qualified for genetic toxicity.

(The following studies were previously reviewed and described in Section 5 of the Unir eview for the referenced NDA 211962)

General Toxicology Studies with the Novel Excipient, NADA

N-acetyl-D-alanine (NADA): A 13-Week Intravenous Infusion Toxicity Study Followed by a 4-Week Recovery Period in Beagle Dogs/ #61717

Beagle dogs were dosed with N-acetyl-D-alanine (NADA) for 13 weeks at 200, 600, and 1800 mg/kg/day intravenously or the vehicle (0.9% NaCl). NADA was generally well tolerated in dogs in daily repeated doses of NADA up to 1800 mg/kg with minimally decreased red blood cell parameters, mildly to moderately increased white blood cell parameters, reversible minimal kidney damage and an increased moderate to severe thrombosis at the infusion site at the high dose. Therefore, the NOAEL was considered 600 mg/kg. The excipient, NADA, was adequately qualified for general toxicity at the clinical dose based on the findings from the study. The NOAEL dose of 600 mg/kg in the dog is 325 mg/kg human equivalent dose (HED) which is approximately 10.8 fold higher than 30.2 mg/kg NADA in a 60 kg human receiving the maximum recommended dose of Xellia Vancomycin at 2 grams based on body surface area comparisons.

N-acetyl-D-alanine (NADA): A 13-Week Intravenous Infusion Toxicity Study Followed by a 4-Week Recovery Period in Sprague-Dawley/ #73831

Sprague-Dawley rats were dosed with NADA for 13 weeks at 560, 1100, and 1680 mg/kg/day intravenously or the vehicle (0.9% NaCl). Repeat dose intravenous NADA injections in rats at the high dose of 1680 mg/kg led to minor enlargement of adrenal glands and kidneys with elevated relative organ weights and increased severity of histopathological changes in the kidney. In high dose females NADA exposures led to persistent changes in the immune system with persistent splenic hematopoiesis and delayed decreases in white cell parameters. The NOAEL was 1100 mg/kg for this study. The excipient, NADA, was adequately qualified for general toxicity at the clinical dose based on the findings from the study. The NOAEL dose of 1100 mg/kg in the rats is 178 mg/kg HED which is approximately 5.9 fold higher than 30.2 mg/kg NADA in a 60 kg human

receiving the maximum recommended dose of 2 grams based on body surface area comparisons.

Embryo-Fetal Development of NADA Excipient
N-acetyl-D-alanine (NADA): Study for Effects on Embryo-Fetal Development in New Zealand White Rabbit by Intravenous Infusion Administration/ LF72KH

Pregnant New Zealand White Rabbits were dosed with 560, 1680, and 3780 mg/kg NADA or vehicle from gestation days (GD) 6-19. Fetuses were removed on GD 29 by cesarean section. NADA was not well tolerated in pregnant rabbits administered 3780 mg/kg. These animals exhibited neurological (tremors, unsteady gait, hypoactivity) and respiratory (abnormal breathing) adverse clinical signs. Excessive urination and drinking were also noted in pregnant rabbits in the 1680 mg/kg group. Five dams were sacrificed early due to evidence of abortion. Fetal exposure to NADA IV led to major fetal cardiovascular abnormalities and major and minor skeletal abnormalities at ≥ 1680 mg/kg. Fetuses in the 1680 mg/kg group were observed to have major cardiovascular abnormalities including dilated ascending aortic arch, ventricular septal defect, major skeletal abnormalities including scoliosis, and minor skeletal abnormalities including branched ribs, additional costal cartilage, delayed ossification of metacarpals/phalanges, and increased cranial ossification of jugal to maxilla. Fetuses in the 3780 mg/kg group were noted with major cardiovascular abnormalities including truncus arteriosus, membranous ventricular septal defect and misshapen heart and minor skeletal abnormalities including delayed ossification of metacarpals/metatarsals/phalanges. No body weight changes were observed in pregnant animals or fetuses. The NOAEL for maternal toxicity was 1680 mg/kg and NOAEL for embryo-fetal toxicity was 560 mg/kg. The NOAEL dose for maternal toxicity of 1680 mg/kg NADA is equivalent to 545 mg/kg HED based on body surface area comparisons which is approximately 18-fold higher than 30.2 mg/kg NADA in a 60 kg human receiving the maximum recommended dose of Xellia Vancomycin at 2 grams. The NOAEL dose for embryo-fetal toxicity of 560 mg/kg NADA is equivalent to 181 mg/kg HED based on body surface area comparisons or approximately 6-fold higher than 30.2 mg/kg NADA in a 60 kg human receiving the maximum dose of Xellia Vancomycin at 2 grams.

N-acetyl-D-alanine (NADA): Study for Effects on Embryo-Fetal Development in Sprague Dawley [Crl:CD(SD)] rat by Intravenous Infusion Administration/ PT59XC

Pregnant Sprague-Dawley rats were dosed with 560, 1680, and 3780 mg/kg NADA or vehicle from GD 6-17. Fetuses were removed by cesarean section on GD 20. Maternal toxicity was not observed; however, NADA increased full litter resorption and fetal developmental anomalies including misshapen margin scapulae, interparietal fissures at ≥1680 mg/kg, and malpositioned testis at 3780 mg/kg. No body weight changes were observed in pregnant animals or fetuses. The NOAEL for maternal toxicity and embryo-fetal toxicity was 1680 mg/kg NADA. This dose in rats corresponds to a 272 mg/kg HED based on body surface area comparisons or approximately 9-fold higher than 30.2 mg/kg NADA in a 60 kg human receiving the maximum dose of Xellia Vancomycin at 2 grams.

Embryo-Fetal Development of Polyethylene Glycol 400 (PEG 400) Excipient
PEG 400: Embryo-fetal Toxicity Study in the New Zealand White Rabbit /DG90YB

Pregnant New Zealand White Rabbits were dosed with 500, 1000, and 2000 mg/kg polyethylene glycol 400 (PEG 400) from GD 6-19. Fetuses were removed on GD 29 by cesarean section. Maternal toxicity was not observed at any dose. In fetuses, major skeletal malformations including lumbar and thoracic scoliosis and minor variations including delayed or incomplete ossification of cranial fontanelles, pubes, epiphyses, and talus bones were noted at 2000 mg/kg. The NOAEL for maternal toxicity was 2000 mg/kg PEG 400. This dose in rats corresponds to a HED of 648 mg/kg based on body surface area comparisons and is approximately 8.6-fold higher than 75.3 mg/kg PEG 400 in a 60 kg human receiving the maximum dose of Xellia Vancomycin at 2 grams. The NOAEL for embryo-fetal toxicity was 500 mg/kg PEG 400. A 500 mg/kg dose in rats corresponds to a 162 mg/kg HED which is approximately 2.2-fold higher that 75.3 mg/kg PEG 400 in a 60 kg human receiving the maximum recommended dose of 2 grams Xellia Vancomycin.

Reviewer's Comments: Due to the embryo-fetal effects observed in nonclinical safety studies from exposure to NADA and PEG 400, the Clinical review team included a boxed warning and warning in the product labeling, recommending that pregnant women not be prescribed Xellia Vancomycin Injection due to the risk of embryo-fetal toxicity.

(b) (4)

. For the referenced NDA 211962, the Pharmacology/Toxicology Reviewer, Dr. Madisa Macon, concluded that the excipients, NADA and PEG 400, posed a potential risk to pregnancy due to concerning findings of malformations from nonclinical embryo-fetal toxicity studies and the relatively high amounts of both excipients in the drug product (NDA 211962). Based on body surface area comparisons and the estimated levels of NADA and PEG 400 in a maximum recommended dose of 2 grams vancomycin in humans, adverse embryo-fetal effects for NADA in rabbits and rats were observed at 6- and 7-fold the clinical dose and 5-fold the clinical dose for PEG 400 in rabbits in Xellia Vancomycin (NDA 211962). Xellia Vancomycin for NDA 213895 contains less NADA and PEG 400 in the to-be-marketed formulation than the referenced Xellia Vancomycin (NDA 211962). For NDA 213895, adverse embryo-fetal effects for NADA in rabbits and rats were observed at 18- and 20-fold the clinical dose and 9-fold the clinical dose for PEG 400 in rabbits based on body surface area comparisons and the estimated levels of NADA and PEG 400 in 2 grams of vancomycin. (b) (4)

, the Agency's Guidance for Industry on Reproductive and Developmental Toxicities –

Integrating Study Results to Assess Concerns[2] states that there is increased concern when there is a positive signal at safety margins <10 and less/decreased concern at safety margins >25. The safety factors (based on the NOAELs) to the maximum clinical dose (based on body surface area) for these effects for NDA 213895 were 6- and 9-fold higher for NADA and 2.2-fold higher for PEG 400, which are within the level of increased concern based on the referenced FDA Guidance. Therefore, the theoretical risk of embryo-fetal effects from PEG 400 and NADA remains and the inclusion of a boxed warning for NDA 213895 is supported from a Pharmacology/Toxicology perspective.

[2] FDA Guidance on Reproductive and Developmental Toxicities – Integrating Study Results to Assess Concerns https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reproductive-and-developmental-toxicities-integrating-study-results-assess-concerns

6 Clinical Pharmacology

6.1. Executive Summary

No clinical pharmacology studies were submitted in this application, and the proposed labeling in relevant clinical pharmacology sections conforms with the approved labeling for the LD ANDA 060180.

6.2. Summary of Clinical Pharmacology Assessment

The Applicant submitted a biobridge request in support of the intravenous route and a biowaiver/biobridge request for use of the parenteral form for the oral route of administration in accordance with 21 CFR 320.24(b)(6). There are no original clinical pharmacology studies conducted to assess the pharmacokinetics of Vancomycin Injection that support this NDA. Please refer to the biopharmaceutical review in the OPQ section of this review for further evaluation of the decision regarding the request for a biobridge to the intravenous route and biowaiver/biobridge to the oral route.

7 Sources of Clinical Data and Review Strategy

No clinical trials were conducted by the Applicant for this NDA. The clinical review consisted of an evaluation of the literature submitted by the Applicant, primarily related to the safety of vancomycin. No statistical review was required for this NDA.

7.1. Review Strategy

Safety Review Approach:

The Applicant states that they performed a review of the scientific literature which covered a period of 1 year before the last update to the LD's Prescribing Information, i.e., from November 2016 until the closest possible date before the NDA submission. In addition, a search of the FDA Adverse Events Reporting System (FAERS) was conducted to identify post marketing safety findings associated with the use of vancomycin. Publications with relevant vancomycin safety information identified for the respective time period were mostly clinical study reports, retrospective reviews, and case reports. The Applicant's safety review is summarized below.

Literature:

Nephrotoxicity (generally defined as changes from baseline in serum creatinine or creatinine clearance) is the most serious adverse event of vancomycin. When used alone and in the absence of other factors that can affect renal function, the rate of nephrotoxicity ranges from 5 to 19% (Gyssens IC et al., 2018).

Risk factors for nephrotoxicity include the dose and duration of vancomycin treatment, serum trough concentrations, patient characteristics, and concomitant receipt of nephrotoxic drugs. (Jeffres MN, 2017 and Lacave G et al., 2017). There is considerable variation in the incidence of nephrotoxicity across studies; however, a recent report indicated an incidence rate of approximately 20%. (Lacave G et al., 2017). The incidence of vancomycin related acute kidney injury (AKI) has been reported as 8.1% (Luther MK et al., 2018) 12% (Tujjar O et al., 2017), 15.1% (Choi YC et al., 2017), 16.2% (Pan K et al., 2017), 29% (Lacave G et al., 2017) and 31.4% (Carreno JJ et al., 2016), depending on the patient population and AKI criteria.

A systematic review and meta-analysis of randomized controlled trials and cohort studies for the period between 1990-2015 concluded that although intravenous vancomycin treatment is associated with a higher risk of kidney injury (vancomycin is the cause of AKI in 59% of vancomycin treated patients), the magnitude of the effect is modest (RR=2.45). This is still much lower than the risk of kidney injury associated with well recognized nephrotoxins, such as aminoglycosides (RR, 8–10) and conventional (nonliposomal) amphotericin B (RR, 4–10). (Nolin TD, 2016)

There is significant correlation between vancomycin trough serum concentrations and the incidence of vancomycin-associated nephrotoxicity. The incidence of AKI decreased from 16.3% to 4.7% after a vancomycin trough monitoring protocol was introduced (Smith AP, 2016).

In addition to high serum trough levels of vancomycin, other risk factors for vancomycin-induced nephrotoxicity include weight- based dosing in obese patients (Choi YC et al., 2017), duration of therapy, and ICU admission (Lacave G et al., 2017).

It has been shown that the combination of vancomycin with other agents, e.g., piperacillin-tazobactam, contributes to higher risk of nephrotoxicity (Peyko V, 2017; Giuliano CA, 2016; Rutter WC, 2017; Allison et al., 2017; Choi YC et al., 2017) with an incidence of up to 46% for the combination therapy.

Ototoxicity is another serious adverse reaction that can be caused by vancomycin. It has been reported mostly in patients who have been given excessive vancomycin doses, have underlying hearing loss, or are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside.

There are literature reports of vancomycin-induced cases of IgA- mediated bullous dermatosis (Winn AE et al., 2016; Castellanos-Gonzales M et al., 2016; Pereira AR et al., 2016) or Henoch-Schönlein purpura (Min Z et al. 2017). Other skin manifestations, such as acute generalized exanthematous pustulosis (Totonchy MB et al., 2016; Pinho A et al., 2017) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (Mattoussi N et al2017; Lam BD et al., 2017) have been reported with vancomycin administration.

Cases of vancomycin-induced thrombocytopenia (Kalra K et al., 2016; Yamanouchi J et al., 2016), delayed TSH elevation in neonates (Zung et al., 2017), and adverse effects on microbiota (Ferrer M et al., 2017; Gasparrini AI et al., 2016) have been described.

Off-label use of intracameral vancomycin (Hsing et al., 2016; Ehmann DS et al., 2017; Andreanos K et al., 2017) has been linked to cases of hemorrhagic occlusive retinal vasculitis (HORV) (Witkin AJ et al., 2017 and Bala C et al., 2016). A warning has been added to the proposed package insert to address this adverse event.

FDA Adverse Events Reporting System (FAERS) data:

The Applicant assessed FAERS data to identify post marketing safety findings associated with the use of vancomycin.These analyses focused on safety findings associated with use of the marketed vancomycin products, LD and generics, covering the time period from December 1, 2016 (1 year before last PI for LD, ANDA # 060180 has been approved) through the most recent available data in FAERS at the time of data request, i.e., June 11, 2019. These were cases in which vancomycin was identified as a suspect medication (cases with vancomycin designated as concomitant medication were excluded from the analysis).

A total of 8545 case reports containing vancomycin adverse events were identified in FAERS for the time period from December 1, 2016 to June 11, 2019. However it should be taken into

account that some of these cases may be duplicate reports. The most frequently reported adverse events are listed in the table below:

Table 7: Most Frequent Adverse Events in FAERS, December 1, 2016 - June 11, 2019

System Organ Classification (SOC)	Preferred Term (PT)	N (%)
Blood and lymphatic system disorders	thrombocytopenia	256 (3.0%)
Gastrointestinal disorders	Diarrhea	192 (2.2%)
General disorders and administration site conditions	drug ineffective	828 (9.7%)
	pyrexia	437 (5.1%)
	condition aggravated	222 (2.6%)
	drug interaction	196 (2.3%)
	multiple organ dysfunction syndrome	190 (2.2%)
Immune system disorders	drug hypersensitivity	751 (8.8%)
	linear IgA disease	246 (2.9%)
Infections and infestations	sepsis	182 (2.1%)
	C. difficile infection	176 (2.1%)
Renal and urinary disorders	acute kidney injury	1288 (15.1%)
	renal tubular necrosis	210 (2.5%)
	nephropathy toxic	201 (2.3%)
	renal failure	193 (2.3%)
Respiratory disorders	dyspnea	182 (2.1%)
Skin and subcutaneous tissue disorders	drug rash with eosinophilia and systemic symptoms (DRESS)	606 (7.1%)
	Rash	393 (4.6%)
	pruritus	232 (2.7%)
	rash maculo-papular	176 (2.1%)

The majority of reported adverse events belonged to the General disorders and administration site conditions, Renal and urinary disorders, and Skin and subcutaneous system disorders. These findings are in line with safety reports presented in the reviewed literature during the period of review. Patients receiving vancomycin often have serious underlying medical conditions which predispose them to bacterial infections; therefore, a number of the reported events could be associated with underlying clinical conditions and/or effects from medications other than vancomycin.

Reviewer's Comment: The reviewer agrees with the Applicant's safety review of the literature and FAERS data for vancomycin products with intravenous administration. Acute kidney injury (AKI) or nephrotoxicity is the most common adverse reaction associated with vancomycin use. The safety review did not reveal any new potential safety signals for vancomycin with intravenous administration. The most common adverse reactions associated with vancomycin by oral adminsitration include nausea, abdominal pain, and hypokalemia. An information

request has been sent to the Applicant to discuss the adverse reactions associated with oral administration.

7.2 Conclusions and Recommendations

This vancomycin product has the potential to cause embryo-fetal toxicity due to the PEG 400 and NADA excipients. The prescribing information for this product should include a Boxed Warning that this formulation of vancomycin injection is not recommended for use during pregnancy because it contains the excipients PEG 400 and NADA, which caused fetal malformations in animal reproduction studies. If use of vancomycin is needed during pregnancy, use of other available formulations of vancomycin is recommended. This information will also be included as a Warning in section 8.1. of the PI.

A complete response action will be taken for NDA 213895, Vancomycin Injection, 5 gm per 100 mL, based on the recommendations of the OPQ/CMC and Nonclinical Pharmacology/Toxicology teams.

8 Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting for this application and no external consultations were sought for this application.

9 Pediatrics

On September 20, 2019, the Applicant submitted a pediatric waiver request. PREA does not apply as the proposed product is not a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

10 Labeling Recommendations

Based on review of this vancomycin product which has the potential to cause embryo-fetal toxicity due to the PEG 400 and NADA excipients, labeling will include a Boxed Warning to describe the risk of embryo-fetal toxicity associated with this formulation of vancomycin. This formulation of vancomycin injection is not recommended for use during pregnancy because it contains the excipients PEG 400 and NADA.

10.1. Prescribing Information (PI)

Reviewer's Comment: Please note that the reviewer's proposed significant labeling changes (below) are high level changes and not necessarily direct quotations from the PI.

Table 8: Summary of High-level Labeling Changes

Summary of Significant Labeling Changes		
Section	**Applicant's Proposed Labeling**	**FDA Recommended Labeling**
HIGHLIGHTS OF PRESCRIBING INFORMATION	(b) (4)	A Boxed Warning was added to describe the risk of embryo-fetal toxicity associated with this formulation of vancomycin. It is not recommended for use during pregnancy because it contains the excipients polyethylene glycol 400 (PEG 400) and N-acetyl-D-alanine (NADA), which caused fetal malformations in animal reproduction studies. If use of vancomycin is needed during pregnancy, use other available formulations of vancomycin.
Reviewer's Comment: The Division recommended the Boxed Warning because this formulation of Vancomycin Injection contains the excipients polyethylene glycol (PEG 400) and N-acetyl D-alanine (NADA), which caused fetal malformations in animal reproduction studies. The Division also recommended that if use of vancomycin is needed during pregnancy, other available formulations of vancomycin should be used.		

Summary of Significant Labeling Changes		
1 INDICATIONS AND USAGE	The proposed indications were the same as the LD including septicemia, infective endocarditis, skin and skin structure infections, bone infections, lower respiratory tract infections; *C. difficile* associated diarrhea (for oral administration only); and Enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) (for oral administration only).	
Reviewer's Comment: The treatment indications remained consistent with the listed drug. The new name of Clostridioides difficile is applied here which replaced the old name of Clostridium difficile.		
2 DOSAGE AND ADMINISTRATION	• Dosing instructions were not adequately delineated by route of administration and patient age.	• Dosing instructions were further delineated by route of administration and patient age.

Summary of Significant Labeling Changes		
Reviewer's Comment: The Dosage and Adminstration section was updated to provide adequate instructions delineated by route of administration and patient age.		
3 DOSAGE FORMS AND STRENGTHS	• The strength provided by the Applicant for this pharmacy bulk package is 50 mg/mL.	• Further characterization of the pharmacy bulk package was provided
Reviewer's Comment: This new formulation for Vancomycin Injection is supplied in a 5 g/100 mL pharmacy bulk package bottle as a clear, colorless to light yellow or light brown solution containing 50 mg/mL of vancomycin.		
5 WARNINGS AND PRECAUTIONS	(b) (4)	• This formulation of Vancomycin Injection is not recommended during pregnancy because it contains the excipients (PEG 400 and NADA), which caused fetal malformations in animal reproduction studies. • Embryo-Fetal toxicity due to PEG400 and NADA excepients is added to Warnings and Precautions. • Wanings and Precautions delineated by route of administration. • The contents of Warnings and Precautions are revised based on the relative clinical significance of the adverse reactions.

Reviewer's Comment: Section 5. Warnings and Precautions has been revised by re-ordering the contents to reflect the relative clinical significance of the adverse reactions and delineated by route of administration.		
6 ADVERSE REACTIONS	No separation of adverse reactions for the two routes of administration.	Specific adverse reactions related to intravenous and oral administration of vancomycin are stated in the PI.
Reviewer's Comment: Section 6 (Adverse Reactions) has been revised based on the Section 5 (Warnings and Precautions) contents for consistency and clarity. The M.O. has requested that the Applicant augment the list of adverse reactions associated with oral administration. This will likely be addressed in the Applicant's response to the CR.		
8 USE IN SPECIFIC POPULATIONS	• The Applicant drafted this section in PLLR format; (b) (4)	• Relevant subsections were revised based on the findings in the animal reproduction studies with the excipients PEG 400 and NADA, which caused fetal malformations.
Reviewer's Comment: Revisions to the PLLR subsections were made based on input from DPMH and the Pharmacology/Toxicology review team.		
16 HOW SUPPLIED/STORAGE AND HANDLING	• Minimal information was provided.	• Additional information was provided for the description of the product and packaging configuration.
Reviewer's Comment: Revisions made to increase clarity regarding the description of the product and packaging configuration.		

Summary of Significant Labeling Changes		
17 PATIENT COUNSELING INFORMATION	(b) (4)	• Risk of Embryo-Fetal Toxicity: Advise patients to notify their healthcare provider if they are pregnant prior to treatment with this formulation of vancomycin.
Reviewer's Comment: This formulation for Vancomycin Injection is not recommended for use in pregnancy because it contains the excipients PEG 400 and NADA, which caused fetal malformations in animal reproduction studies.		

11 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

12 Postmarketing Requirements and Commitment

None.

13 Division Director (Clinical) Comments

I concur with the review team's assessment and recommendations.

14 Appendices

14.1. References

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14.2. Financial Disclosure

No clinical trials were conducted by the Applicant; therefore, no financial disclosure report was submitted.

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/s/

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