

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211962Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA 211962 - Multi-Disciplinary Review and Evaluation

Application Type	NDA 505(b)(2)
Application Number	211962
Priority or Standard	Priority
Submit Date	May 23, 2018
Received Date	May 23, 2018
PDUFA Goal Date	November 23, 2018; February 19, 2019 (following major amendment)
Division	DAIP
Review Completion Date	February 19, 2019
Established Name	Vancomycin hydrochloride
Trade Name	Vancomycin Injection
Pharmacologic Class	Glycopeptide antibacterial
Code name	N/A
Applicant	Xellia Pharmaceuticals ApS
Formulation(s)	Single-dose flexible bags: 500 mg/100 mL, 1 g/200 mL, 1.5 g/300mL, and 2 g/400 mL
Dosing Regimen	Adult Patients: 2 g divided either as 0.5 grams (g) every 6 hours or 1 g every 12 hours Pediatric Patients (1 month and older): 10 mg/kg per dose given every 6 hours
Applicant Proposed Indication(s)/Population(s)	• Septicemia • Infective Endocarditis • Skin and skin structure infections • Bone infections • Lower respiratory tract infections
Regulatory Action	Approval
Recommended Population(s)	Adults (except pregnant women) and Pediatrics (except neonates)

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Reviewers of Multi-Disciplinary Review and Evaluation

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NDA Multi-Disciplinary Review and Evaluation – NDA 211962

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OPDP=Office of Prescription Drug Promotion

DMEPA=Division of Medication Error Prevention and Analysis

DPMH=Division of Pediatrics and Maternal Health

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DAIP	Division of Anti-infective Products
DMC	data monitoring committee
ECG	electrocardiogram
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
GLP	good laboratory practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
LD	Listed Drug
MedDRA	Medical Dictionary for Regulatory Activities
micro-ITT	microbiological intent-to-treat
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
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
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
TEAE	treatment emergent adverse event
TEADR	treatment emergent adverse reaction
USPI	US prescribing information
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

Xellia Pharmaceuticals ApS submitted NDA 211962 Vancomycin Injection 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL under section 505(b)(2) of the FDCA. The reference listed drug (RLD) is Vancocin hydrochloride in plastic container, 500 mg/100 mL, 750 mg/150 mL and 1 g/200 mL approved in NDA 50671 (Vancomycin Injection, USP, in Galaxy plastic container) held by Baxter Healthcare Corporation approved April 1993 (500 mg/mL and 1 g/200 mL) and December 20, 2010 (750 mg/mL). The active ingredients, indications, route of administration, and dosage form are the same as those of the RLD. The proposed product is a liquid, ready-to-^{(b) (4)} vancomycin formulation stable to be stored below 25°C (77°F), while the RLD is a frozen product stored at or below -20°C (-4°F) that requires thawing prior to use. The proposed product has excipients that are different from the RLD ^{(b) (4)}.

No new clinical studies were conducted to support this application. Nonclinical studies were performed to assess the toxicity of the excipients N-acetyl-D-alanine (NADA) and polyethylene glycol 400 (PEG 400) that are new and not in the RLD. Based on the potential risk of embryo-fetal toxicity based on the findings in the nonclinical studies, the labeling for this vancomycin product includes a Boxed Warning and a Warning regarding the risk of fetal toxicity. Additionally, because this formulation of Vancomycin Injection is supplied in single-dose flexible bags, it should be used only in patients who require the entire (500 mg, 1 g, 1.5 g or 2 g) dose and not any fraction thereof. Therefore, the product will not include labeling for administration to neonates.

The application has been granted Fast Track and Qualified Infectious Disease Product designations.

1.2. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In NDA 211962, the Applicant is seeking approval of Vancomycin Injection 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL under section 505(b)(2) of the FDCA. The listed drug is Vancocin hydrochloride in plastic container (NDA 50671, Vancomycin Injection, USP, in Galaxy plastic container). The drug product is a ready for single use plastic bag presentation for intravenous administration. The proposed product has excipients that are not in the listed drug (b) (4). Also, the Applicant's proposed drug product includes two dose strengths that are not found with the listed drug: 1.5 g/300 mL and 2 g/400 mL.

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 most common adverse reactions associated with vancomycin are anaphylaxis, "red man syndrome" (or infusion-related reactions), acute kidney injury, hearing loss, and neutropenia. Vancomycin injection, in a ready for single use plastic bag presentation for intravenous use contains the following excipients: NADA, L-lysine hydrochloride (L-Lys), PEG 400, hydrochloric acid, sodium hydroxide and water. Reproduction studies in rabbits with intravenous doses of PEG 400 at approximately 5 times the maximum daily human dose based on body surface area comparisons administered during organogenesis resulted in fetal spinal malformations. Reproduction studies in rabbits and rats using intravenous doses of NADA at approximately 6 and 7 times the maximum daily human dose, 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 is also included as a Warning and is described in section 8.1. Use in pediatric patients is described under the DOSAGE AND ADMINISTRATION section which advises health care providers to use this product only in pediatric patients who require the entire contents of the single-dose flexible bag and not any fraction thereof. (b) (4) this product is not appropriate for use in neonates

since the lowest available strength of 500 mg is not appropriate for neonates.

In conclusion, approval of this 505(b)(2) NDA, Vancomycin Injection, in a ready for single use plastic bag presentation for intravenous administration is supported by the previous FDA findings of effectiveness and safety of Vancomycin Injection in Plastic Container (NDA 50671). Additionally, the efficacy and safety review of published literature, review of the product quality (chemistry, manufacturing and controls) information, and animal pharmacology and toxicology information support approval of this NDA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	CDC reports that in the U.S. 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.	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.	Unlike other vancomycin drug products currently on the market which are either lyophilized or frozen pre-mixed products, this product does not require any additional preparation prior to use which may reduce the risk of medication errors and time required for IV solution preparation.
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 Injection provides benefit as it may be more conveniently stored (without refrigeration or freezing) and it does not require any additional preparation prior to use which may reduce the risk of medication errors and time required for IV solution preparation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• 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. • The fixed dose strengths of 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL may exceed dosing requirements for younger pediatric populations. This product should only be used in pediatric patients if it is appropriate to administer the entire bag and not a fraction of it.	• This vancomycin product has the potential to cause embryo-fetal toxicity due to the PEG 400 and NADA excipients. • Use of this product in the pediatric population should be limited to those who need the contents of the entire bag and not a fraction of it.
Risk Management	• The prescribing information for this product includes 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 is also included as a Warning and is described in section 8.1. The use in pediatric patients is described in the Dosage and Administration section of the Vancomycin Injection PI stating: “Use this formulation of Vancomycin Injection only in pediatric patients who require the entire dose (500 mg, 1 g, 1.5 g or 2 g) of this single-dose flexible bag and not any fraction of it.”	

Regulatory Background

2.1. U.S. Regulatory Actions and Marketing History

The Applicant has submitted this 505 (b)(2) New Drug Application for Vancomycin Injection, 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL, in ready for single use plastic containers for intravenous use with the same active ingredients, indications, route of administration, dosage form and dosing regimen as the reference listed drug (RLD), Baxter's vancomycin injection, in Galaxy plastic container, NDA 050671, initially approved in 1993. The RLD is provided in the following dose strengths: 500 mg/ 100 ml, 750 mg/150 ml, 1 g/200 ml. Of note, the proposed product has two additional strengths: 1.5 g/300 mL, 2 g/400 mL. The Applicant's proposed product has excipients different from the RLD (b) (4)

2.2. Summary of Presubmission/Submission Regulatory Activity

Pre-IND 131664 for Vancomycin Injection was reviewed by DAIP on July 25, 2016.

The individual reviews from different disciplines are in DARRTS for this pre-IND submission. Specifically, the Agency had concerns regarding two excipients: PEG 400 and N-acetyl-D-alanine (NADA). PEG 400 is used in other approved products, but not in antibacterial drugs; while NADA is a novel excipient and had not been qualified in any previously approved products by the Agency.

Vancomycin Injection, 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL was granted Qualified Infectious Disease Product Designation on February 9, 2018 for the following indications:

- Treatment of serious or severe infections caused by susceptible isolates of methicillin-resistant (beta-lactam resistant) staphylococci
- Treatment for penicillin-allergic patients and patients who cannot receive or who have failed to respond to other drugs, including the penicillins or cephalosporins
- Treatment of infections caused by vancomycin-susceptible organisms that are resistant to other antimicrobial drugs
- Treatment of staphylococcal endocarditis
- Treatment of infections due to staphylococci, including septicemia, bone infections, lower respiratory tract infections, skin and skin structure infections
- Treatment of diphtheroid endocarditis
- Treatment of endocarditis caused by *Streptococcus viridans* or *Streptococcus bovis*
- Treatment of endocarditis caused by *Enterococci* in combination with aminoglycosides

In addition, Vancomycin Injection, 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL was granted Fast Track Designation on July 12, 2018; and therefore, the NDA received a priority review.

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

3.1. Office of Scientific Investigations (OSI)

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

3.2. Product Quality

Novel excipients: Yes

N-acetyl-D-alanine (NADA) is a non-compendial and a novel excipient. A satisfactory specification that includes tests for (b) (4) is provided for NADA. The Pharmacology Toxicology team has found the proposed NADA impurity limits to be acceptable. More information is found in a DMF that has been reviewed and found to be adequate. All other excipients are compendial and comply with the requirements of the USP/NF monographs.

Any impurity of concern: No

Sufficient controls to insure safety and efficacy of the commercial product: Yes

Vancomycin is a tricyclic glycopeptide derived from *Amycolatopsis orientalis* (previously *Nocardia orientalis*). The drug product, a ready to use vancomycin injection for intravenous infusion, is provided in single-dose containers of 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL, and 2 g/400 mL.

Based on satisfactory stability data, the proposed expiration dating period of 16 months when stored below 25°C is acceptable. Given the pronounced trends towards lower purity and higher impurities, the applicant has committed to making future expiration extensions by means of a CBE-30 supplement rather than an Annual Report.

Because the composition of the proposed to-be-marketed parenteral drug product is not qualitatively and quantitatively (Q1/Q2) the same as that of the RLD due to the presence (b) (4) (N-acetyl-D-alanine and L-lysine hydrochloride) and (b) (4) (polyethylene glycol 400), a biowaiver per 21 CFR § 320.22(b)(1) is not feasible. Per 21 CFR 320.24(b)(6), the Applicant's proposed drug product has been adequately bridged to the RLD; therefore, an in-vivo bioavailability study, comparing the RLD to the proposed drug product, is not needed.

The single-dose container closure system is designed to maintain product sterility and the microbiological quality of the drug product. The integrity of the proposed container-closure system is validated.

All Product Quality aspects including facilities are found acceptable.

Table 1: Drug Product Composition

Name of ingredient	Quantity per unit					Function	Reference to Standard
	500 mg/ 100 mL	1 g /200 mL	1.5 g /300 mL	2 g /400 mL	Percentage		
Vancomycin (b) (4) ^a	0.5 g	1.0 g	1.5 g	2.0 g	0.5 % (w/V)	Active substance	In house
N-acetyl-D-alanine	1.36 g	(b) (4)				(b) (4)	In house
L-lysine Hydrochloride (Monochloride)	1.26 g	2.52 g	3.78 g	5.04 g	1.26 % (w/V)	(b) (4)	USP
Polyethylene glycol 400	1.8 mL	3.6 mL	5.4 mL	7.2 mL	1.8% (V/V)		NF
Hydrochloric acid	q.s. ¹	q.s. ¹	q.s. ¹	q.s. ¹	q.s.	pH adjusting agent	NF
Sodium hydroxide	q.s. ²	q.s. ²	q.s. ²	q.s. ²	q.s.	pH adjusting agent	NF + In house
Water for Injection	q.s. 100 mL	q.s. 200 mL	q.s. 300 mL	q.s. 400 mL	NA	(b) (4)	USP
Compressed Air ³	q.s.	q.s.	q.s.	q.s.	NA	Processing aid	In house

NA – Not Applicable

^a An overfill of (b) (4)% is employed for manufacture of Vancomycin Injection, 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL to ensure administration of labelled amount of active (for more details on set Overfill please refer to Section 3.2.P.2.2 within 3.2.P.2 Pharmaceutical Development).

(b) (4)

(b) (4)

(b) (4)

3.3. Devices and Companion Diagnostic Issues

Not applicable.

4. Nonclinical Pharmacology/Toxicology

4.1. Executive Summary

The Applicant, Xellia Pharmaceuticals ApS, conducted a 13-week comparative toxicology and toxicokinetic study in dogs with Xellia's Vancomycin Injection (also referred to as Xellia Vancomycin Injection in this review) (containing L-lysine, PEG 400 and NADA) and the RLD Baxter's Vancomycin Injection (also referred to as Baxter Vancomycin Injection in this review), and an in vitro human blood compatibility and hemolytic potential study with Xellia Vancomycin Injection. Based on the overall findings from these nonclinical studies, Xellia Vancomycin Injection appears comparable in its general toxicity and toxicokinetic profile to the RLD Baxter Vancomycin Injection and lacks concern for hemolytic potential. The Applicant also conducted several nonclinical studies to assess the safety of PEG 400 and the novel excipient, NADA. The Applicant will rely on the Agency's prior findings of safety for vancomycin, as well as the nonclinical information in labeling of FDA approved vancomycin products to support the current NDA, as permitted under section 505(b)(2) of the Food, Drug, and Cosmetic Act.

Xellia Vancomycin Injection is a new formulation with vancomycin that contains three excipients not included in the RLD Vancomycin Injection: L-lysine, polyethylene glycol (PEG) 400, and N-acetyl-D-alanine (NADA). L-lysine is a common excipient that is a component of other previously approved FDA products for intravenous administration at higher amounts. PEG 400 is a common excipient found in other previously approved FDA products for intravenous administration, however, the amount of PEG 400 in the Xellia drug product is higher than in other approved products (7.2 mL of PEG 400 or 8.1 grams based on a density of 1.126 g/mL for the maximum recommended dose of 2.0 grams of vancomycin). For comparison, a chemotherapeutic drug for intravenous injection contains a slightly lower amount of PEG 400 when administered at the maximum recommended human dose but is indicated for a shorter treatment duration. Following recommendations from the Division, the Applicant conducted a Segment 2 embryo-fetal and developmental toxicity study with PEG 400 in rabbits to address a gap in safety data within the published literature. As NADA is a novel excipient not used in previously approved FDA products, the Applicant conducted a full battery of nonclinical safety studies to qualify the excipient including primary, secondary, and safety pharmacology, repeat-dose toxicology, genetic toxicology, and reproductive and developmental toxicology studies. Based on the findings of these studies, the toxicity of NADA was adequately assessed for use in Xellia Vancomycin Injection.

Pharmacokinetics

The systemic exposure of vancomycin in Xellia's Vancomycin Injection was comparable to that of the RLD Baxter Vancomycin Injection with C_{max} of 146-159 $\mu\text{g/mL}$ vs 158-159 $\mu\text{g/mL}$ on Day 91, respectively, and AUC of 374-391 $\mu\text{g}\cdot\text{hr/mL}$ vs 392- 446 $\mu\text{g}\cdot\text{hr/mL}$ on Day 91, respectively, indicating that the excipients L-lysine, NADA, and PEG 400 did not alter the TK profile of vancomycin. The plasma steady-state of Xellia Vancomycin was 0.38 L/kg in dogs, which was

similar to the comparator Vancomycin Hydrochloride Injection USP (Xellia APS) at 0.35 L/kg at the same dose of 30 mg/kg. There was no evidence of accumulation. No studies were conducted with Xellia Vancomycin Injection to determine the distribution, metabolism, or excretion of this formulation.

From a literature review for PEG 400, following intravenous administration, PEG 400 is rapidly excreted in the urine unchanged with recovery up to 67% in rabbits¹ and up to 88% in dogs². PEG 400 was found to be excreted mainly via glomerular filtration.^{1,3,4}

Safety Pharmacology

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

Repeat-Dose Toxicology /Comparative Nonclinical Toxicology

The toxicity and toxicokinetics of Xellia's Vancomycin Injection were compared to the RLD Baxter Vancomycin in a 13 week repeat dose toxicity study in dogs. The kidneys were identified as the main target of toxicity in the Vehicle Control, Xellia's Vancomycin Injection, and Baxter Vancomycin groups. At 75/100 mg/kg of Xellia's Vancomycin Injection and Baxter Vancomycin, similar incidence and severity of renal glomerulonephritis and minimal to mild tubular degeneration/necrosis/regeneration were observed. Lymphoid erythro-phagocytosis and splenic extramedullary hematopoiesis observed in Vehicle Control, Baxter Vancomycin, and Xellia's Vancomycin Injection animals suggest hemolysis. Increased thrombi were noted at the site of injection in both Vehicle Control and Xellia's Vancomycin Injection groups compared with Saline controls. Although the incidence and severity of kidney toxicity and/or inflammation in dogs treated with Xellia's Vancomycin Injection appeared slightly greater than in dogs treated with Baxter's Vancomycin at the same dose levels, these findings were minimal and considered equivocal when both groups were compared to the Saline and Vehicle Control groups. Vancomycin exposures in dogs were approximately 2-2.5 times the exposure in humans at the recommended human dose for vancomycin based on mean plasma concentrations.

¹ Schaffer C, Critchfield F, Nair J, 1950, The absorption and excretion of a liquid polyethylene glycol. J Am Pharm Assoc Sci Ed, 39:340–344.

² Herold DA, Keil K, Bruns DE, 1989, Oxidation of polyethylene glycols by alcohol dehydrogenase. Biochem Pharmacol, 38:73-76.

³ Deutsche Forschungsgemeinschaft (DFG), 2012 Polyethylene glycol. The MAK collection for Occupational Health and Safety, (10) 248-270.

⁴ Chadwick VS, Phillips, SF, Hofmann, AF, 1977, Measurements of intestinal permeability using low molecular weight polyethylene glycols (PEG 400). Gastroenterology, 73:241-246.

In a literature review, PEG 400 showed dose related evidence of toxicity by IV administration. In dogs, acute exposure was associated with hypotension and apnea at $\geq 3\text{g/kg}$.³ Following repeated IV dosing of PEG 400 in rats for 4 weeks, toxicity included increased respiratory rate, increased reticulocyte count, and increased local inflammation at the injection site at 2500 mg/kg.³ PEG 400 administered to rabbits for 5 weeks at approximately 350 mg/kg resulted in one death with increased BUN, and cloudy swelling of renal tubular epithelium parenchyma.⁵ Dogs dosed with IV PEG 400 up to 8.45 g/kg for 30 days resulted in dry mouth and dry nasal mucosa at 6.34 g/kg and cloudy swelling of kidney cells and increased glomerular volume at 8.45 g/kg.⁶ Baboons dosed for 29 days up to 1000 mg/kg PEG 400 via IV administration led to weight loss in one high dose female.³

Genetic Toxicology and Carcinogenicity

No genetic toxicology studies were conducted Xellia's Vancomycin Injection. From the labeling of the RLD, vancomycin alone was not found to be mutagenic based on standard laboratory tests. The standard laboratory tests for genotoxicity in the RLD vancomycin labeling were not described. No carcinogenicity studies were conducted with vancomycin.

Reproductive Toxicology

No reproductive toxicology studies were conducted with Xellia's Vancomycin Injection. From the labeling of the RLD Vancomycin product, when vancomycin was administered to pregnant rats or rabbits during organogenesis at 200 mg/kg/day IV or 120 mg/kg/day IV (equivalent to the maximum recommended human dose), no effects on fetal body weight or development were observed. Maternal toxicity was observed in rats (at doses $\geq 120\text{ mg/kg}$) and rabbits (at doses $\geq 80\text{ mg/kg}$).

No definitive studies have been conducted with vancomycin to determine its effects on fertility or pre/postnatal development.

From a review of the published nonclinical literature, PEG 400 was found to reduce female fertility when orally administered to rats at 2.8 g/kg/day during mating, gestation, and lactation.⁷ Mating, copulatory interval, gestation length, and embryofetal development were unaffected. To further qualify the excipient PEG 400, the Applicant conducted an embryofetal toxicity study in rabbits. In pregnant rabbits dosed up to 2000 mg/kg/day IV PEG 400 during GD

⁵ Smyth HF, Carpenter CP, Shaffer CB, 1947. The toxicity of high molecular weight polyethylene glycols; chronic oral and parenteral administration. J Am Pharm Assoc, (36):157-160.

⁶ Li BQ, Dong X, Fang SH, Gao JY, Yang GQ, Zhao H, 2011, Systemic toxicity and toxicokinetics of a high dose of polyethylene glycol 400 in dogs following intravenous injection. Drug Chem Tox 34(2):208–212.

⁷ The European Agency for the Evaluation of Medicinal Products (EMA), 1995, Committee for Veterinary Medicinal Products: Polyethylene Glycols. MRL/034

6-19, fetal spinal abnormalities including scoliosis and minor skeletal variations were reported with no effect on fetal body weights or maternal outcomes. The NOAEL for fetal toxicity was 500 mg/kg or 162 mg/kg HED with a safety factor approximately 1.2 times higher than the estimated amount of PEG 400 in the maximum human clinical dose of Xellia's Vancomycin Injection based on body surface area comparisons.

To qualify the excipient NADA, embryo-fetal toxicity studies were conducted in rats and rabbits. In pregnant rabbits dosed with ≥ 1680 mg/kg/day IV NADA during organogenesis (GD 6-19) resulted in major cardiovascular and major and minor skeletal abnormalities in fetuses. These effects were observed with and without evident maternal toxicity (≥ 1680 mg/kg). The NOAEL for fetal toxicity was 560 mg/kg or 181 mg/kg HED with a safety factor of approximately 2 times higher than the presumed amounts of NADA in the maximum human clinical dose of Xellia's Vancomycin Injection based on body surface area comparisons. In rats, exposure to 3780 mg/kg/day IV during organogenesis (GD 6-17) led to minor skeletal variations and malpositioned testis in fetuses. However, these effects were observed at maternally toxic doses and therefore their toxicological relevance is uncertain. The NOAEL for maternal and fetal toxicity in rats was 1680 mg/kg or 272.2 mg/kg HED with a safety factor of approximately 3 times higher than the presumed amount of NADA in the maximum human clinical dose of Xellia's Vancomycin Injection based on body surface area comparisons.

Other Toxicology

Xellia's Vancomycin Injection was compatible with human serum and plasma and did not show potential for hemolysis.

RECOMMENDATION

The Applicant has provided sufficient nonclinical safety information on this formulation of Vancomycin Injection to support its marketing in the U.S. based on the toxicity and toxicokinetic bridging study to the RLD Baxter Vancomycin. All other excipients were adequately qualified based on higher amounts in previous FDA approved products or assessed for safety in the submitted nonclinical studies. From a pharmacology/toxicology perspective, there are no objections to the approval of this NDA. Recommendations for changes to the pharmacology/toxicology relevant sections of the labeling were provided to the Applicant.

4.2. Referenced NDAs, BLAs, DMFs

IND 131664, DMF (b) (4), NDA 050671

4.3. Pharmacology

Primary pharmacology

The Applicant conducted an in vitro comparative study to determine the effects of Xellia's Vancomycin Injection (containing L-Lysine, NADA, PEG 400) and Baxter's Vancomycin on

bacterial growth. See section 8.1 Executive Summary in the Clinical Microbiology section of the review.

Secondary Pharmacology

No secondary pharmacology studies were conducted with Xellia's Vancomycin Injection.

Safety Pharmacology

No safety pharmacology studies were conducted with Xellia's Vancomycin Injection.

4.4. ADME/PK

Studies were conducted to compare the toxicokinetic (TK) parameters of Xellia's Vancomycin Injection and the RLD Baxter Vancomycin. Comparative TK data from the 13-week intravenous comparative toxicology study in Beagle Dogs are included in the table below. TK data of excipients alone were measured in pregnant New Zealand White Rabbits exposed to PEG 400 or NADA in embryofetal toxicology studies; data are included in the table below.

Table 2. Toxicology Studies

Type of Study	Major Findings
TK data from comparative toxicology study <i>Comparative Intravenous Infusion Study with Xellia Vancomycin, 0.5% and Baxter Vancomycin, 0.5%; 13 weeks in dogs; Study #62155</i> - Dogs dose with 75 mg/kg daily from Day 1-59 then 100 mg/kg daily from Day 60-91 - Samples collected predose, 30 and 60 minutes post start of infusion, and 5, 15, 30, 60 minutes, and 2, 4, 8, 24 hours post end of infusion	<u>Dog Xellia Vancomycin Injection</u> <i>T_{1/2}: 1.56- 5.12 hours</i> Day 1 C _{max} : 123 mcg/mL Day 1 AUC _{0-Tlast} : 239 mcg*hr/mL Day 45 C _{max} : 111 mcg/mL Day 45 AUC _{0-Tlast} : 229 mcg*hr/mL Day 91 C _{max} : 152 mcg/mL Day 91 AUC _{0-Tlast} : 371 mcg*hr/mL <i>Accumulation: No accumulation up to Day 45</i> <i>Sex Related Differences: No</i> <u>Dog Baxter Vancomycin Injection (RLD)</u> <i>T_{1/2}: 1.85-4.57 hours</i> Day 1 C _{max} : 133 mcg/mL Day 1 AUC _{0-Tlast} : 307 mcg*hr/mL Day 45 C _{max} : 120 mcg/mL Day 45 AUC _{0-Tlast} : 256 mcg*hr/mL Day 91 C _{max} : 159 mcg/mL Day 91 AUC _{0-Tlast} : 404 mcg*hr/mL <i>Accumulation: No accumulation up to Day 45</i> <i>Sex Related Differences: No</i> -----

Type of Study	Major Findings
- TK of Vancomycin in Xellia Vancomycin Injection does not appear to be different from Vancomycin TK in the RLD Baxter Vancomycin Injection - TK data from male and female dogs were combined.	<u>Excipients: Xellia Vancomycin Injection (NADA and PEG 400)</u> <u>TK of NADA in Xellia Vancomycin Injection</u> <i>T_{1/2}: 0.88-3.58 hours</i> Day 1 C_{max}: 423 mcg/mL Day 1 AUC_{0-Tlast}: 718 mcg*hr/mL Day 45 C_{max}: 381 mcg/mL Day 45 AUC_{0-Tlast}: 654 mcg*hr/mL Day 91 C_{max}: 514 mcg/mL Day 91 AUC_{0-Tlast}: 1934 mcg*hr/mL <i>Accumulation: No accumulation up to Day 45</i> <i>Sex Related Differences: No</i> <u>TK of PEG 400 in Xellia Vancomycin Injection</u> <i>T_{1/2}: 1.52-5.19 hours</i> Day 1 C_{max}: 512 mcg/mL Day 1 AUC_{0-Tlast}: 949 mcg*hr/mL Day 45 C_{max}: 456 mcg/mL Day 45 AUC_{0-Tlast}: 877 mcg*hr/mL Day 91 C_{max}: 589 mcg/mL Day 91 AUC_{0-Tlast}: 1270 mcg*hr/mL <i>Accumulation: No accumulation up to Day 45</i> <i>Sex Related Differences: No</i>

Type of Study	Major Findings																								
TK of the excipient NADA from Embryofetal Toxicity Study in Rabbits <i>N-Acetyl-D-Alanine (NADA): Study for Effects on Embryo-Fetal Development in the New Zealand White Rabbit by Intravenous Infusion Administration; Study #LF72KH</i> • 0, 560, 1680 mg/kg daily • Samples collected 1, 3, 24 hour after start of infusion	Table 3. Toxicokinetic Parameters for NADA in Rabbit Plasma on Gestation Day 6 and 19 <table><tr><th rowspan="2">Dose level (mg/kg/day)</th><th colspan="2">C_{max} (µg/mL)</th><th colspan="2">AUC₂₄ (µg.h/mL)</th></tr><tr><th>GD 6</th><th>GD 19</th><th>GD 6</th><th>GD 19</th></tr><tr><td>560</td><td>973</td><td>857</td><td>4050</td><td>4120</td></tr><tr><td>1680</td><td>2890</td><td>2770</td><td>13400</td><td>12300</td></tr></table> <i>Accumulation: None</i> <i>Dose Proportion: Approximately proportional</i>	Dose level (mg/kg/day)	C _{max} (µg/mL)		AUC ₂₄ (µg.h/mL)		GD 6	GD 19	GD 6	GD 19	560	973	857	4050	4120	1680	2890	2770	13400	12300					
Dose level (mg/kg/day)	C _{max} (µg/mL)		AUC ₂₄ (µg.h/mL)																						
	GD 6	GD 19	GD 6	GD 19																					
560	973	857	4050	4120																					
1680	2890	2770	13400	12300																					
TK of the excipient PEG 400 from Embryofetal Toxicity Study in Rabbits <i>PEG 400: Embryofetal Toxicity Study in the New Zealand White Rabbit; Study# DG90YB</i> • 0, 500, 1000, 2000 mg/kg PEG 400 daily • Samples collected 5, 30 minutes, and 2, 4, 8, and 23.5 hours after completion of infusion	Table 4. Toxicokinetic Parameters for PEG 400 in Rabbit Plasma on Gestation Day 6 and 19 <table><tr><th rowspan="2">Dose level (mg/kg/day)</th><th colspan="2">C_{max} (µg/mL)</th><th colspan="2">AUC₂₄ (µg.h/mL)</th></tr><tr><th>Day 6</th><th>Day 19</th><th>Day 6</th><th>Day 19</th></tr><tr><td>500</td><td>815</td><td>532</td><td>1100</td><td>935</td></tr><tr><td>1000</td><td>1630</td><td>1340</td><td>2250</td><td>2380</td></tr><tr><td>2000</td><td>3630</td><td>2910</td><td>5820</td><td>5470</td></tr></table> <i>Accumulation: None</i> <i>Dose Proportion: Approximately proportional</i>	Dose level (mg/kg/day)	C _{max} (µg/mL)		AUC ₂₄ (µg.h/mL)		Day 6	Day 19	Day 6	Day 19	500	815	532	1100	935	1000	1630	1340	2250	2380	2000	3630	2910	5820	5470
Dose level (mg/kg/day)	C _{max} (µg/mL)		AUC ₂₄ (µg.h/mL)																						
	Day 6	Day 19	Day 6	Day 19																					
500	815	532	1100	935																					
1000	1630	1340	2250	2380																					
2000	3630	2910	5820	5470																					

4.5. Toxicology

4.5.1. General Toxicology

4.5.1.1. Comparative Nonclinical Toxicology

A 13-Week Comparative Intravenous Infusion Toxicity Study with Xellia's Vancomycin, 0.5% and Baxter's Vancomycin, 0.5% Followed by a 4-Week Recovery Period in Beagle Dogs

Key Study Findings

- Toxicity of Xellia's Vancomycin Injection was considered similar to the toxicity of the RLD Baxter's Vancomycin Injection when administered to dogs for 13 weeks. Slight differences in hemolysis, thrombosis, and kidney toxicity were noted in Xellia's Vancomycin Injection animals compared to Baxter's Vancomycin animals.
- Toxicokinetic values for vancomycin did not appear different in animals treated with Xellia's Vancomycin Injection compared with the reference drug Baxter's Vancomycin, suggesting that the vehicle formulation of Xellia's Vancomycin Injection did not affect the systemic properties, including exposure, of vancomycin.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	Saline Control, Vehicle, Baxter Vancomycin 75/100 mg/kg, Xellia Vancomycin 75/100 mg/kg (Dose increased on Day 60)
Route of administration:	Intravenous Injection (1-hour infusion) via a catheter surgically inserted into the femoral vein
Formulation/Vehicle:	Baxter Vancomycin 5mg/mL in excipient; Xellia Vancomycin 5 mg/mL in 13.6 mg/mL (N-acetyl-D-alanine (NADA), 12.6 mg/mL L-lys-HCl, and 20.3 mg/mL PEG 400 in sterile water; Xellia Vehicle 13.6 mg/mL (N-acetyl-D-alanine (NADA), 12.6 mg/mL L-lys-HCl, and 20.3 mg/mL PEG 400 in sterile water
Species/Strain:	Beagle Dog ((b) (4))
Number/Sex/Group:	5/sex/group Main Study
Age:	6-7 months
Satellite groups/ unique design:	Recovery Period 2/sex/group; Increased dose from 75 to 100 mg/kg Vancomycin on Day 60
Deviation from study protocol affecting interpretation of results:	Yes: Two animals were euthanized early that did not meet euthanasia criteria due to Applicant's assessment

of poor health.

Table 5. Observations and Results: changes from control (saline)

Parameters	Major findings
Mortality	One VC female and one XV female were euthanized due to Applicant's assessment of poor deteriorating clinical condition on Day 85 and 86 respectively
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Food Consumption	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	VC: ↓RBC 20%, ↓ HGB 21%, ↓HCT 21%, ↑%Reticulocytes 57% in males and females; ↓WBC 48%, ↓ Neut 49%, ↓Lymph 49%, ↓Baso 59%, ↓LUC 70% in females compared with C @13 Weeks; RBC, HGB, HCT at recovery suggesting feedback BV: ↓WBC 37%, ↓ NEUT 45% @ 6 weeks in Males XV: ↓WBC 29%, ↓ Monocytes 37 % @ 6 weeks in Males
Clinical Chemistry	Unremarkable
Urinalysis	VC: Increased amount of blood and protein content XV: Increased blood and protein content; moderate to severe sedimentation of epithelial cells in females that remained following the recovery phase
Gross Pathology	XV: Dark discolored lymph nodes, infusion site gelatinous material or thickening XV: kidney discoloration (2/9), enlarged or discolored lymph nodes, infusion site gelatinous material or thickening BV: kidney discoloration (7/10), enlarged, discolored, or mottled lymph nodes, infusion site gelatinous material or thickening Single VC female terminated early: enlarged and pale kidneys Single XV female terminated early: pale kidneys; discolored lymph nodes
Organ Weights	Unremarkable

Parameters	Major findings
Histopathology Adequate battery: Yes/No	VC: Hemolysis with lymphoid erythrophagocytosis, and splenic extramedullary hematopoiesis, bone marrow hypercellularity; increased thrombi at infusion site BV: Hemolysis with lymphoid erythrophagocytosis, and splenic extramedullary hematopoiesis XV: Hemolysis with lymphoid erythrophagocytosis, and splenic extramedullary hematopoiesis; minimal bilateral degeneration/necrosis of renal proximal tubular epithelium and minimal bilateral regeneration of the renal proximal tubular epithelium, hemolysis; increased thrombi and thickening at infusion site VC female terminated early: mild bone marrow hypercellularity, splenic extramedullary hematopoiesis, thymic atrophy, renal glomerular proliferative inflammation* and interstitial inflammation, minimal endocarditis XV female terminated early: Hemolysis with lymphoid erythrophagocytosis, and splenic extramedullary hematopoiesis, lung fibrosis, thymic atrophy, renal glomerular proliferative inflammation*, Hyaline droplets, mild bilateral degeneration/necrosis of proximal tubular epithelium and mild bilateral regeneration of proximal tubular epithelium
Extended Kidney histopathology* (Select C, BV, and XV animals [5/group] were evaluated from additional tissue slides.)	BV: Mild cortical focal necrosis (1/5); minimal interstitial fibrosis (4/5); mild arteritis (1/5) XV: Mild to moderate cortical focal necrosis (2/5); moderate glomerulonephritis (1/5)
Additional Notes*	• According to the Applicant all glomerulonephritis was considered to be early signs of age-related chronic kidney disease • No thrombi observed in lungs in any group • A different pathologist reviewed the extended kidney histopathology slides

C: saline control; VC: vehicle control; BV: Baxter Vancomycin; XV: Xellia Vancomycin.

-: indicates reduction in parameters compared to control.

Reviewer's Comment: The reviewer does not agree with the Applicant that the majority of the kidney findings were due to an age-related or background kidney disease in the dogs; the Investigators did not provide any evidence to rule out the treatment effects of the Vehicle Control, Xellia Vancomycin, or Baxter Vancomycin. While kidney disease does appear frequently in dogs⁸, the dogs in this study were young <1 year old at the end of the study. While one saline control animal was noted to have a single mild cortical infarct from the extended kidney histopathology, the majority of kidney effects were observed in VC, BV, and XV groups. Therefore, it is more likely that the effects were related to VC, BV, or XV treatment. In addition, the VC and XV females that were euthanized early did not meet the euthanasia criteria described in their laboratory protocol per se, but were euthanized early due to the reported occurrence of adverse clinical observations late in the study. The study protocol was amended by the Applicant to include an additional time-point for blood collection at Week 10 to evaluate specific clinical chemistry parameters of creatinine and urea. Collected blood from this new timepoint indicated that these two animals had higher creatinine and urea than in their respective groups and compared with controls, suggesting minor kidney injury. It is possible that these data prompted the termination of dosing in these animals and, when combined with the reported "deteriorating clinical conditions", led the Investigators to euthanize these animals prematurely despite failing to meet the standard euthanasia criteria. Further, the creatinine and urea levels were normal at the pre-dosing period of the study, which does not support the Investigators' theory that the kidney disease preceded treatment in these two animals. It is the reviewer's opinion that the vehicle control containing NADA and PEG 400 may have adversely affected the kidneys. Had the vehicle control group been included in the extended histopathological analysis, or Xellia Vancomycin Injection been tested at a higher dose, the potential differences in toxicity with PEG 400 and NADA may have been more apparent when compared to the RLD Baxter Vancomycin.

4.5.1.2. General toxicology; additional studies

Hemolytic Potential of Xellia Vancomycin 0.5%

Xellia Vancomycin 0.5%: Hemolytic Potential and Compatibility Study in Human Blood Using Xellia Vancomycin 0.5%/51034

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 at matrix:formulation ratios of 1:1, 1:0.25, and 1:0.1 (v:v). There was no precipitation or coagulation observed in serum or plasma incubated with Xellia Vancomycin Injection at room temperature. Hemolysis was not observed in the whole blood incubated with Xellia Vancomycin Injection. Therefore, 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.

⁸ Robertson JL, 1986, Spontaneous Renal Disease in Dogs. Toxicol Path, 14 (1): 101-108.

4.5.2. Genetic Toxicology

No genetic toxicology studies were conducted with Xellia Vancomycin Injection.

4.5.3. Carcinogenicity

No carcinogenicity studies were conducted with Xellia Vancomycin Injection.

4.5.4. Reproductive and Developmental Toxicology

No studies were conducted to assess the reproductive or developmental potential of Xellia Vancomycin Injection. The Applicant conducted embryofetal development studies to qualify the novel excipient, NADA (rat and rabbit), and the high levels of PEG 400 (rabbit only) in Xellia Vancomycin Injection. See Section 5.5.5 Other Toxicology Studies below.

4.5.5. Other Toxicology Studies

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

Key Study Findings

- NADA was generally well tolerated in beagle dogs in daily repeat dose of NADA up to 1800 mg/kg with minimally decreased red blood cell measurements, mildly to moderately increased white blood cell measurements, 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 is qualified for general toxicity at the clinical dose; 600 mg/kg in the dog is 325 mg/kg HED (approximately 3.6 times higher than 90.5 mg/kg NADA in a 60 kg human receiving the maximum dose of Xellia Vancomycin Injection at 2 g based on body surface area comparisons).

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 200, 600, 1800 mg/kg/day NADA once per day
Route of administration:	Intravenous Injection, 2-hour infusion via a catheter surgically implanted into the femoral vein
Formulation/Vehicle:	NADA in 0.9% NaCl for injection
Species/Strain:	<i>Canis familiaris</i> , Beagle

Number/Sex/Group: Five/sex/group
 Age: 7 months old
 Satellite groups/ unique design: Recovery group; 2/sex/control and 1800 mg/kg NADA group/ Conducted in 3 blocks of animals
 Deviation from study protocol affecting interpretation of results: No

Table 6. Observations and Results: changes from control

Parameters	Major findings
Mortality	No mortalities
Clinical Signs	Reduced fecal output in NADA treated dogs
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
ECG <i>[delete the row for rodents]</i>	Unremarkable
Hematology	HD females: ↓ HGB 12.8%, ↓ HCT 13.6% HD males: Following the recovery period, ↑ WBC 89.9%, ↑ neutrophils 110%, ↑ lymphocytes 32.4%, and ↑ monocytes 177%
Clinical Chemistry	Unremarkable
Urinalysis	Unremarkable
Gross Pathology	HD: Increased moderate/severe thrombosis and thickening at infusion site
Organ Weights	Unremarkable
Histopathology Adequate battery: Yes	HD: Increased moderate/severe thrombosis with/without severe necrosis at infusion site; increased minimal to mild hypercellularity of bone marrow; increased lymphoid hypercellularity

LD: low dose; MD: mid dose; HD: high dose.

:- indicates reduction in parameters compared to control.

Reviewer's Comments: The Applicant did not consider the effects at 1800 mg/kg to be adverse and determined the NOAEL at 1800 mg/kg.

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

Key Study Findings

- Repeat dose intravenous NADA injections in rats at the high dose of 1680 mg/kg led to minor enlargement of adrenal gland and kidneys with elevated relative organ weights and increased severity of histopathological changes. In high dose females NADA exposures led to persistent changes in immune system with persistent splenic hematopoiesis and delayed decreases in white cell parameters. The NOAEL is considered 1100 mg/kg in this study.
- The excipient NADA is qualified for general toxicity at the clinical dose based on these findings in rats; 1100 mg/kg in the rat is 178 mg/kg HED (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 based on body area surface comparisons).

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 560, 1100, 1680 NADA Once Daily
Route of administration:	Intravenous Injection (2 hour infusion) via a cannula surgically implanted into the femoral vein
Formulation/Vehicle:	N-acetyl-D-alanine (NADA) in 0.9% saline
Species/Strain:	Sprague Dawley Crl:CD (SD) rats (b) (4)
Number/Sex/Group:	18/sex/control group; 21/sex/NADA treated groups
Age:	10 weeks old
Satellite groups/ unique design:	Recovery group (5/sex/control and high dose group)
Deviation from study protocol affecting interpretation of results:	No

Table 7. Observations and Results: changes from control

Parameters	Major findings
Mortality	There were no mortalities related to NADA*
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
Hematology	Unremarkable during dosing. Recovery HD Females: ↑ Neut (3 fold), ↑ Mono (1.8 fold), ↑ % Neut (2 fold), ↑ % Mono (1.4 fold), ↑ % Luc (1.4 fold), ↓ % lymph (-25%)
Clinical Chemistry	Recovery HD Females: ↑ globulin (1.3 fold)
Urinalysis	Unremarkable
Gross Pathology	HD: Enlarged adrenals, kidney, pituitary glands, and spleen; Gelatinous material in prostate
Organ Weights	HD: Increased relative adrenal (32 %) and kidney (16%) weights in males; Dose dependent increased in relative kidney weights in females up to 24%. HD Recovery Females: Increased relative liver (27%) and kidney weights (19%)
Histopathology Adequate battery: Yes	Dose dependent increase in splenic cortical hypertrophy; kidney tubular basophilia; liver Kupffer cell hypertrophy, periportal necrosis; lymphoid hypercellularity and plasmacytosis; splenic extramedullary hematopoiesis, lymphoid hypercellularity; infusion site thrombosis, peri/vascular inflammation, and lumen necrosis. Recovery HD: Splenic hematopoiesis
Additional comments*	• 24 rats were found dead or euthanized early including animals in control and NADA treated groups that was likely due to problems with the catheter or the infusion procedure • Quality of study affected by the catheter procedure

LD: low dose; MD: mid dose; HD: high dose.

-: indicates reduction in parameters compared to control.

Reviewer's Comments: The Investigators did not consider the effects at 1680 mg/kg to be adverse and determined the NOAEL to be 1680 mg/kg.

Genetic Toxicology with the Novel Excipient, NADA

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Bacterial Reverse Mutation Assay of N-Acetyl-D-Alanine (NADA)/304570

Key Study Findings: Negative

GLP compliance: Yes

Test system: *S. typhimurium* strains TA98, TA100, TA1535, and TA1537; *E. coli* strain WP2 uvrA; 0.16, 0.31, 0.63, 1.3, 2.5, 5.0 mg NADA/plate; +/- S9

Study is valid: Yes

In Vitro Assays in Mammalian Cells

In Vitro Chromosomal Aberration Test of N-Acetyl-D-Alanine (NADA) in Chinese Hamster Ovary (CHO) Cells/304571

Key Study Findings: Negative

GLP compliance: Yes

Test system: Chinese Hamster Ovary (CHO-WBL) cells; 0.5, 1.0 2.0 mg/mL NADA; +/- S9

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

N-acetyl-D-alanine (NADA): In vivo Rat Micronucleus Test Using Peripheral Blood Reticulocytes/55440

Key Study Findings: Negative

GLP compliance: Yes, except for use of dose at 3780 mg/kg which is higher than the standard limit dose of 2000 mg/kg in ICH S2(R1) and OECD 474 guidelines

Test system: Sprague-Dawley Crl:CD (SD), bone marrow nuclei; 0, 560, 1680, 3780 mg/kg NADA

Study is valid: Yes

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

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 was 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 $\geq$ 1680 mg/kg.
- The NADA 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 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).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 560, 1680, 3780mg/kg/day PEG 400

Route of administration: Intravenous injection (2-hour infusion) via a catheter surgically implanted into the marginal ear vein

Formulation/Vehicle: NADA in 0.9% NaCl for injection

Species/Strain: New Zealand White Rabbit (b) (4)

Number/Sex/Group: 30 mated females per group

Satellite groups: None

Study design: Pregnant dams were dosed daily from Gestation Day (GD) 6-19, fetuses removed by cesarean section on GD 29; studies conducted in 3 uneven blocks as follow

Group	Treatment	Dose# mg/kg/day	Cohorts	Number of animals
1	Control	0	1 to 3	24
2	NADA	560	1 to 3	25
3	NADA	1680	1 to 3	26
4	NADA	3780	1 only	5

Deviation from study protocol affecting interpretation of results: Yes; Only 1 block of animals dosed with 3780 mg/kg NADA group due to extreme toxicity noted at this dose.

Table 8: Observations and Results

Parameters	Major findings
Mortality	One MD and one HD were sacrificed early due to welfare reasons on GD 9 and 7, respectively. Animals were noted to have underactive behavior. MD animals was noted to have abnormal breathing
Clinical Signs	MD: Increased urination during dose and excessive drinking following dosing HD: Increased urination during dose and excessive drinking following dosing, body tremors, unsteady gait, underactive behavior and abnormal breathing; Only 1 block of 7 dams received HD NADA
Body Weights	Maternal body weights unremarkable (in surviving dams in LD and MD); fetal body weights unremarkable
Food Consumption	Unremarkable
Necropsy findings Cesarean Section Data	Unremarkable
Necropsy findings Offspring (See Tables 9 and 10; Table 16 in Appendix 1)	MD: Major cardiovascular abnormalities including dilated ascending aorta arch, ventricular septal defect; additional visceral abnormality of enlarged lobe in thyroid; Minor skeletal abnormalities including, branched rib, additional costal cartilage, metacarpals/phalanges, and increased cranial ossification of jugal to maxilla HD: Major cardiovascular abnormalities including truncus arteriosus, membranous ventricular septal defect and misshapen heart; Minor skeletal delays in ossification of metacarpals/metatarsals/phalanges

LD: low dose; MD: mid dose; HD: high dose; HC: historical controls

Reviewer's Comments: Five dams were sacrificed early due to evidence of abortion. In the 3780 mg/kg group, several of the animals were noted to have excessive urination, excessive drinking, body tremors, unsteady gait, underactive behavior and abnormal breathing. The Investigators believed these adverse clinical signs were not appropriate for the study yet could not rule out an effect of treatment. Similar adverse clinical signs were observed in dogs dosed up to 1800 mg/kg in the cardiovascular safety pharmacology study with NADA. It is also possible that adverse clinical observations may have been related to the large amount of NADA administered to the dams or due to complications of the infusion procedure. Notably, no adverse clinical observations were noted at doses ≥ 3780 mg/kg NADA in a pilot study. Due to the severity of the maternal effects observed in the HD dams, the Investigators/Applicant did not dose the

remaining animals in the HD group. Due to the severe maternal toxicity and low number of surviving dams/fetuses in the HD group, interpretation of the embryo-fetal effects of NADA at this dose was limited. Adverse clinical signs in pregnant dams did not affect maternal body weight, uterine weight, food consumption, maternal macropathology, fetal survival, litter size or fetal body weights.

Fetal malformations noted in NADA-treated animals including major cardiovascular abnormalities in MD and HD litters. Although low in incidence, these effects were not observed in concurrent controls and exceeded the historical control mean and range (Table 9). In addition, scoliosis (cervical and lumbar) was higher in the 1680 mg/kg group compared with controls with 2 affected litters out of 22 total litters (Table 10). It is possible that the scoliosis may have been observed at higher doses had the investigators tested at a dose between the mid and high dose. Higher incidence of scoliosis was also observed with PEG 400 exposure in rabbit. Increased minor skeletal variations in MD fetuses included branched rib, additional costal cartilage; delayed ossification of metacarpals/phalanges was increased in MD and HD groups; delayed ossification was increased in the few HD fetuses/litters. In addition, amelia, a major defect, was noted in the MD group in 1 fetus in 1 litter. While of low incidence (4.5%; Appendix 1 - Table 16), there are no instances of this rare malformation in fetuses/litters in the concurrent or historical controls for (b) (4) New Zealand White Rabbits (NZW). It is possible that this rare malformation and similar effects would have been observed at higher doses had the Investigators/Applicant tested animals at a dose between the mid and high dose.

Table 9: Litter Incidence of Major Cardiovascular Abnormalities in Mid Dose, High Dose, Concurrent Control, and Historical Control in New Zealand White Rabbits

Malformation	Control	Mid Dose	High Dose	Historical Controls*
	# (%)	# (%)	# (%)	# (%)
Dilated Ascending aorta/aortic arch	0/21 (0%)	2/22 (9.1%)	0/2 (0%)	7/373 (1.9%)
Dorsally displaced pulmonary trunk	0/21 (0%)	1/22 (4.5%)	0/2 (0%)	2/373 (0.3%)
Truncus arteriosus	0/21 (0%)	0/22 (0%)	1/2 (50%)	1/373 (0.3%)
Membranous ventricular septal defect	0/21 (0%)	0/22 (0%)	1/2 (50%)	3/373 (0.8%)
Muscular ventricular septal defect	0/21 (0%)	1/22 (4.5%)	0/2 (0%)	4/373 (1.1%)
Misshapen heart	0/21 (0%)	0/22 (0%)	1/2 (50%)	2/373 (0.5%)

Values in bold indicate higher incidence in treated compared with concurrent or historical controls, albeit non-statistically; #: number affected litter/total litters; %: percent of total; *: Combination of (b) (4) Historical Control data submitted in the Final Study Report and following further discussion with the Agency.

Table 10: Litter Incidence of Scoliosis in Mid Dose, Concurrent Control, and Historical Control in New Zealand White Rabbits

Malformation	Control	Mid Dose	Historical Control*
	# (%)	# (%)	# (%)
Cervical scoliosis	0/21 (0%)	1/22 (4.5%)	0/373 (0%)
Lumbar Scoliosis	0/21 (0%)	1/22 (4.5%)	3/373 (0.8%)
Total scoliosis	0/21 (0%)	2/22 (9.1%)	3/373 (0.8%)

Values in bold indicate higher incidence in treated compared with concurrent or historical controls, albeit non-statistically; #: number affected litter/total litters; %: percent of total; *: Combination of (b) (4) Historical Control data submitted in the Final Study Report and following further discussion with the Agency.

Although these major fetal abnormalities were observed at maternal toxic doses it was concluded by the reviewer that a NADA treatment effect could not be ruled out. It is likely that minor skeletal variations were secondary to NADA maternal toxicity.

In the Final Study report, the study investigators highlighted fetal heart and major blood vessel abnormalities in MD and HD litters. Although maternal toxicity was observed in both groups, the Applicant concluded that the fetal cardiovascular effects may have been related to NADA

exposure. No other effects were originally considered related to NADA exposure by the Applicant.

After further discussions with the Division, the Applicant submitted additional assessments of this study based on updated historical control data and from the Applicant's reproductive and developmental expert. In the secondary assessments by the Applicant and the Applicant's expert, they concluded that there were no embryo-fetal effects due to NADA and that the updated NOAEL for embryo-fetal effects was the MD 1680 mg/kg. The cardiovascular congenital effects observed in the MD group were concluded to have been within the historical control range based on % fetuses affected per litter. Also, the Applicant grouped the finding of 'multiple vertebral and rib abnormalities' with 'scoliosis' for fetal vertebral abnormalities with the updated (b) (4) NZW historical control dataset. The Applicant justified the grouping as they believed multiple vertebral/rib abnormalities are often the cause of scoliosis. In the expert's assessment the findings of 'multiple vertebral/rib abnormalities', 'scoliosis' and minor skeletal variations including "malaligned and missing ossification centers" were grouped to determine the overall % fetal incidence/litter for fetal vertebral abnormalities. The expert also noted thoracogastroschisis in one fetus in one litter in the MD group that was overlooked by the Investigators and this reviewer. This fetus also was observed to have multiple major skeletal abnormalities, including scoliosis, minor skeletal variations, and major cardiovascular abnormalities, which he attributed to thoracogastroschisis.

We do not agree with the Applicant's assessment that there are no embryofetal effects associated with exposures to NADA during organogenesis in rabbits. Our assessment of the embryofetal data in the study reports and our comparison with the historical control data of (b) (4) and (b) (4) New Zealand White Rabbits (See Tables 16 and 17 in Appendix 1) is based on recommendations described in ICH Guidances and FDA best practices. It should be noted that the Agency's method of comparison is different from that of the Applicants and the Applicant's expert based on the following:

- 1) Litter incidence should be used as the basic unit of comparison as fetuses within a litter are not considered to be independent of each other. (ICH Guidance S5A)⁹*
- 2) When comparing litter incidences to historical control data, the mean litter incidence of the historical controls across studies and years provided should be compared, according to our reproductive and developmental toxicology (RDT) experts in CDER. For rare fetal abnormalities within historical controls, the study with the maximum litter incidence is often an outlier within the data.*

⁹ ICH Guidance S5A

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074950.pdf>

- 3) *Statistical analysis may not be appropriate when comparing incidence of rare events particularly for developmental studies as they often lack statistical power to determine significance. (FDA Guidance for Industry Reproductive and Developmental Toxicities: Integrating Study Results to Assess Concerns)¹⁰*
- 4) *When determining safety multiples for a nonclinical safety finding, in the absence of measured clinical pharmacokinetic data body surface area comparisons are used.*
- 5) *As recommended by RDT experts, we did not group together the findings “scoliosis” with “multiple vertebral/rib abnormalities” in our assessment. We agree with the Applicant and their expert that some multiple vertebral/rib anomalies may lead to scoliosis, but not all do. Furthermore, scoliosis is considered a rare abnormality, while some vertebral/rib abnormalities may not be. We also did not include associated minor vertebral abnormalities in our assessment of scoliosis.*

Based on the absence of effects on maternal parameters such as maternal body weight and pathology despite clinical observations, the NOAEL for maternal toxicity was determined to be 1680 mg/kg NADA by the reviewer. Based on the increased incidence of fetal scoliosis and cardiovascular abnormalities, the NOAEL for embryo-fetal toxicity was determined to be 560 mg/kg by the reviewer. There is a safety multiple of approximately 6 for maternal toxicity and approximately 2 for embryofetal toxicity based on body surface area comparisons of these NOAELs.

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 and fetal developmental anomalies including misshapen margin scapulae, interparietal fissures at ≥ 1680 mg/kg, and malpositioned testis at 3780 mg/kg NADA.
- The maternal toxicity no observed adverse effect level (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).

¹⁰ FDA Guidance for Industry Reproductive and Developmental Toxicities: Integrating Study Results to Assess Concerns

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079240.pdf>

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 560, 1680, 3780mg/kg/day NADA

Route of administration: Intravenous injection (2-hour infusion) via a catheter surgically implanted into the femoral vein

Formulation/Vehicle: NADA in 0.9% NaCl for injection

Species/Strain: Sprague Dawley Rats

Number/Sex/Group: 21 presumed pregnant animals/group

Satellite groups: None

Study design: Pregnant dams were dosed daily from Gestation Day (GD) 6-17, fetuses removed by cesarean section on GD 20

Deviation from study protocol affecting interpretation of results: No

Table 11: Observations and Results

Parameters	Major findings
Mortality	Seven deaths in NADA treated dams due to infusion procedure and not attributed to NADA administration
Clinical Signs	Unremarkable
Food Consumption	Unremarkable
Body Weights	Unremarkable for maternal and fetal body weights
Necropsy findings Cesarean Section Data	HD: Litter resorption (four dams)
Necropsy findings Offspring	HD: Cranial skeletal abnormalities including misshapen margin scapulae and interparietal fissures; Malpositioned testis in males

LD: low dose; MD: mid dose; HD: high dose; HC: historical controls

Reviewer's Comments: It was difficult to interpret results of the study due to loss of pregnant animals related to the catheterization or infusion procedure. The Investigators concluded that there was an increase in minor skeletal variation of the 14th rib, however the litter incidence at the high dose was 38.5% (5/13) vs 35% (7/20) for the concurrent controls and 37.4% (68/182) for the historical controls. Therefore, the reviewer concluded that these skeletal variations were not due to NADA exposure as they were within historical incidences. Minor cranial skeletal variations were higher in the MD and HD groups. While only 1 litter per group was observed to have each variation, these skeletal variations were noted as they were observed in both dose groups.

Embryo-Fetal Development of Polyethylene Glycol 400 (PEG 400) Excipient

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).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 500, 1000, 2000 mg/kg/day PEG 400

Route of administration: Intravenous injection (30 min infusion) in the marginal vein of alternating ears

Formulation/Vehicle: (b) (4) (PEG 400)/ water for injection

Species/Strain: New Zealand White rabbits (b) (4)

Number/Sex/Group: 1 male/group; 22 females/group

Satellite groups: None

Study design: Pregnant dams were dosed daily from Gestation Day (GD) 6-19, fetuses removed by cesarean section on GD 29

Deviation from study protocol affecting interpretation of results: No

Table 12: Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	Unremarkable
Body Weights	HD: Reduced corrected maternal body weight gain (52.7%); no effect on fetal body weights
Food Consumption	Unremarkable
Necropsy findings Cesarean Section Data	Unremarkable
Necropsy findings Offspring (see Table 13; Table 17 in Appendix 1)	MD: Increase of delayed ossification of vertebrae compared to CC and HC; Increase in cervical scoliosis compared to CC and HC HD: Increase in delayed or incomplete ossification of pubes, epiphyses, and talus bones; increase in lumbar and thoracic scoliosis compared to CC and HC
Additional Comments	The Applicant did not consider the observations in the fetuses at any dose to be adverse and thus set the NOAEL for embryofetal toxicity at 2000 mg/kg.

LD: low dose; MD: mid dose; HD: high dose; CC: concurrent controls HC: historical controls

Reviewer's Comments: Four rabbits were euthanized before the scheduled necropsy: One control for welfare reasons, two controls for suspected abortion, and one MD animal for suspected abortion. The rate of abortion in concurrent controls (10%) was above the rate in historical controls in IV infusion studies of (b) (4) New Zealand White Rabbits ((b) (4)) (2%; 3/122, Table 17 in Appendix 1,).

Due to the loss of control dams, it was difficult to interpret the results of this study. Following in utero exposures, minor fetal skeletal variations were noted by the reviewer in all treated groups and the major skeletal malformation, scoliosis, was noted in MD and HD groups when compared with controls based on litter incidence (Table 13; Table 17 in Appendix 1). The incidences of these minor and major skeletal findings were also higher when compared to historical controls.

Table 13: Litter Incidence of Scoliosis in Mid Dose, High Dose, Concurrent Controls, and Historical Controls in (b) (4) New Zealand White Rabbits

Malformation	Control	Mid Dose 1000 mg/kg	High Dose 2000 mg/kg	Historical Controls 2013-2017*
	# (%)	# (%)	# (%)	# (%)
Cervical/Thoracic scoliosis	0/17 (0%)	1 (5.6%)	1/22 (4.5%)	6/460 (1.3%)
Lumbar Scoliosis	1/17 (5.9%)	0 (0%)	2/22 (9.1%)	0/460 (0%)
Total scoliosis	1/17 (5.9%)	1 (5.6%)	3/22 (13.6%)	6/460 (1.3%)

Values in bold indicate higher incidence in treated compared with concurrent or historical controls, albeit non-statistically; *The Applicant submitted two sets of Historical Controls Data from (b) (4) for New Zealand White Rabbits. The original historical control data submitted in the Final Study Report for DG90YB had 152 total litters. In the second set of historical control data from (b) (4) contained detailed information related to fetal examinations in studies from 2016-2017 with 308 litters total. Both were combined for a total of 460 historical controls litters from 2013-2017. The second set of historical control data from (b) (4) also include non-detailed information from 160 litters from 2013-2015. This information was not sufficient to be incorporated into the review.

In the Final Study report for DG90YB, the study investigators highlighted major and minor skeletal variations in PEG 400 treated groups but did not consider the observations to be adverse. “[M]ultiple vertebral and rib abnormalities” were noted in the HD animals, but were not considered to be related to PEG 400 exposure as they were also observed in concurrent controls. Increased fetal incidences of minor skeletal variations were also observed in MD and HD groups. All minor skeletal findings were not considered adverse per the Investigators as they are transient in nature or were associated with lower fetal body weights. In the Final Study report, the Investigators did not mention differences in incidence of fetal lumbar or cervical/thoracic scoliosis between the treatment and concurrent control groups.

After further discussions with the Division, the Applicant submitted additional data to support their conclusion that there were no adverse maternal or developmental effects observed in this study. The Applicant submitted secondary assessments based on updated robust historical control data and the opinion of the Applicant’s reproductive and developmental expert. In the follow-up assessments, the Applicant grouped the finding of ‘multiple vertebral and rib abnormalities’ with ‘scoliosis’ in comparison of the treatment data with the updated (b) (4) NZW historical control dataset. The Applicant justified the grouping as they believed multiple vertebral/rib abnormalities are often the cause of scoliosis. In the expert’s assessment the findings of ‘multiple vertebral/rib abnormalities’, ‘scoliosis’ and minor skeletal variations including “malaligned and missing ossification centers” were grouped to determine the overall incidence of fetal vertebral abnormalities. Both the Applicant and their expert concluded that there were no maternal or fetal effects of PEG 400 based on lack of statistical differences.

We do not agree with the Applicant's assessment that there are no embryofetal effects associated with exposures to PEG 400 during organogenesis in rabbits. Our assessment of the embryofetal data in the study reports and our comparison with the historical control data of (b) (4) New Zealand White Rabbits is based on recommendations described in ICH Guidances and FDA best practices. It should be noted that the Agency's method of comparison is different from that of the Applicants and the Applicant's expert based on the following:

- 1) Litter incidence should be used as the basic unit of comparison as fetuses within a litter are not considered to be independent of each other. (ICH Guidance S5A)¹¹*
- 2) When comparing litter incidences to historical control data, the mean litter incidence of the historical controls across studies and years provided should be compared, according to our reproductive and developmental toxicology (RDT) experts in CDER. For rare fetal abnormalities within historical controls, the study with the maximum litter incidence is often an outlier within the data.*
- 3) Statistical analysis may not be appropriate when comparing incidence of rare events particularly for developmental studies as they often lack statistical power to determine significance. (FDA Guidance for Industry Reproductive and Developmental Toxicities: Integrating Study Results to Assess Concerns)¹²*
- 4) When determining safety multiples for a nonclinical safety finding, in the absence of measured clinical pharmacokinetic data body surface area comparisons are used.*
- 5) As recommended by RDT experts, we did not group together the findings "scoliosis" with "multiple vertebral/rib abnormalities" in our assessment. We agree with the Applicant and their expert that some multiple vertebral/rib anomalies may lead to scoliosis, but not all do. Furthermore, scoliosis is considered a rare abnormality, while some vertebral/rib abnormalities may not be. We also did not include associated minor vertebral abnormalities in our assessment of scoliosis.*

The NOAEL for PEG 400 maternal toxicity in rabbits was determined to be 2000 mg/kg. This NOAEL results in a 4.8 safety factor with a 648 mg/kg HED (based on body surface area comparisons) at the highest clinical dose. Based on differences in litter incidence in the study and historical control data, this Reviewer concluded that PEG 400 increased the incidence of

¹¹ ICH Guidance S5A

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074950.pdf>

¹² Guidance for Industry Reproductive and Developmental Toxicities: Integrating Study Results to Assess Concerns

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079240.pdf>

minor and major (scoliosis) skeletal variations in a dose-dependent manner compared with controls. The NOAEL for fetal toxicity was determined to be 500 mg/kg of PEG 400 in rabbits following exposures during organogenesis. A NOAEL of 500 mg/kg of PEG 400 in rabbits results in a safety factor of 1.2 based on 162 mg/kg HED (based on body surface area comparisons).

Due to the theoretical risk of the embryo-fetal effects observed in nonclinical safety studies caused by the high volume excipients PEG 400 and NADA in Xellia's formulation for Vancomycin Injection, not present in other vancomycin products, the Clinical review team included a Boxed Warning and Warning in the product labeling, recommending pregnant woman not be prescribed Xellia Vancomycin Injection due to the risk of embryo-fetal toxicity.

5. Clinical Pharmacology

5.1. Executive Summary

No clinical pharmacology studies have been conducted with the Applicant's proposed product; and the proposed labeling in relevant Clinical Pharmacology sections conforms with the approved labeling for the RLD (NDA 211962; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209481s000lbl.pdf).

5.2. Summary of Clinical Pharmacology Assessment

No dedicated clinical pharmacology studies were conducted to assess the pharmacokinetics of Vancomycin Injection. Of note, this product contains three excipients that are not in the RLD: L-lysine, polyethylene glycol (PEG) 400, and N-acetyl-D-alanine (NADA). Both PEG 400 and NADA are primarily excreted in urine. An information request was sent to the Applicant requesting a rationale for the safety of PEG 400 and NADA in patients with renal impairment given concerns of potential excipient accumulation.

In their response, the Applicant proposed that accumulation of NADA and PEG 400 will always be proportionally less than that of vancomycin, which is also eliminated renally and dose reduced in patients with renal impairment. Furthermore, the predicted clearance of NADA and PEG 400 in humans is much higher than that of vancomycin (~4-fold and 13-fold higher, respectively) and the half-lives are much shorter (1.5 hrs for NADA and 0.75 hr for PEG 400) than vancomycin (4 to 6 hr). Based on these data, we agree that it is reasonable to assume patients with renal impairment would not have accumulation of vancomycin, PEG or NADA when dosed appropriately for their level of renal impairment.

The Applicant also stated that the predicted NOAEL:human exposure ratios of PEG 400 are above 7-fold based on the 90-day GLP dog study, and above 2.5-fold based on the 14-day GLP rat study, and are, therefore, adequate to qualify PEG 400 as an excipient at levels present in the vancomycin formulation. See section 5.0 Nonclinical Pharmacology/Toxicology for a comprehensive review of the toxicity and toxicokinetic data with this formulation.

6. Statistical and Clinical Evaluation

6.1. Sources of Clinical Data and Review Strategy

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

No financial disclosure report was provided by the Applicant because no clinical studies were conducted for this application.

7. Clinical Microbiology Review

The antimicrobial susceptibility of representative bacteria to the proposed product (Vancomycin Injection, 5 mg/mL; Xellia) and RLD (Vancomycin injection, USP) was similar using the broth microdilution method. Additionally, NADA, which is structurally similar to the D-alanyl-D-alanine termini in the peptidoglycan layer of Gram positive bacteria, did not inhibit the activity of vancomycin at NADA to vancomycin ratios greater than in the formulation (1000:1 or 125:1).

8. Review of Safety

Safety Review Approach

The Applicant states that they performed a review of the scientific literature to cover the period of 1 year before the last update of the Prescribing Information for the listed drug (September 2016) until the closest possible date before the NDA submission. The search term “vancomycin” was used to identify articles of interest with activated filters “human” and “publication date” (1-September-2016 to 30-March-2018). 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.

8.2. Review of the Safety Database

Overall Exposure

Dosing recommendations for vancomycin include an initial dose of no less than 15 mg/kg, including in patients with mild to moderate renal insufficiency. The Applicant’s proposed drug product includes two dose strengths that are not found with the RLD: 1.5 g/300 mL and 2 g/400 mL. Xellia has included these dose strengths to accommodate for heavier patients, for example, a patient weighing 100 kilograms (220 pounds) would receive 1.5 grams per dose, and a patient weighing 133 kilograms (292 pounds) would receive a dose of approximately 2 grams. The current recommendation of 15 mg/kg is reasonable as a starting dose to achieve therapeutic concentrations. Subsequent doses would be calculated based on therapeutic drug monitoring (TDM), taking the patient’s trough value into account.

8.3. Adequacy of Applicant’s Clinical Safety Assessments

Safety in the Postmarket Setting - Literature Review

Literature data confirm nephrotoxicity (generally defined as changes from baseline in serum creatinine or creatinine clearance) as the most serious adverse event of vancomycin which is usually reversible. 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 concentration, patient characteristics, and concomitant receipt of nephrotoxic drugs. (Jeffres MN, 2017) and ICU patients (Lacave G et al., 2017).

There is a considerable variation in the incidence of nephrotoxicity across studies; however, a recent report noted the incidence at approximately 20% (Lacave G et al., 2017).

A systematic review and meta-analysis of randomized controlled trials and cohort studies for the period 1990-2015 concluded that although intravenous vancomycin 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 (non-liposomal) amphotericin B (RR, 4–10). (Nolin TD, 2016). There is significant correlation between vancomycin trough serum concentrations and the incidence of vancomycin-associated nephrotoxicity. It has been shown that overall incidence of AKI decreased from 16.3% to 4.7% after institution of vancomycin trough monitoring protocols (Smith AP, 2016).

Besides the trough levels of vancomycin, other risk factors for vancomycin-induced nephrotoxicity may include weight-based dosing in obese patients (Choi YC et al., 2017), duration of therapy, and ICU admission (Lacave G et al., 2017). Additionally, 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 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 al 2017; Lam BD et al., 2017) have been reported with vancomycin administration.

Off-label but recently widespread use of intracameral vancomycin (Hsing et al., 2016; Ehmann DS et al., 2017; Andreanos K et al., 2017) have 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 Event Reporting System (FAERS) Data

The Applicant evaluated data from FAERS for reports in which vancomycin was identified as a suspect drug in causing AEs. The Applicant did not review cases in which vancomycin was considered a concomitant (non-suspect) medication in the AE report. These analyses focused on safety findings associated with use of the marketed vancomycin RLD and generic products covering the time period from September 1, 2016 through the second quarter (Q2) of 2017.

A total of 314 reports containing vancomycin adverse events were identified in FAERS for the time September 1, 2016 through Q2 2017. These reports included 983 total adverse events, including 882 events from cases identified as serious, and 101 events from cases identified as non-serious. It should be noted that FAERS contains mainly serious adverse events from 15-days reports, therefore the database probably does not represent an accurate estimate of the incidence of non-serious events.

Of 882 reports identified in FAERS, approximately half (50.0-54.58%) were in males and one-third (37.50-38.56%) in females. Reports in pediatric patients were uncommon; less than 5% in the age <18 years. The majority of reports were in the age group of 18-65 years old (46.17%) and in the elderly (36.30%). The most frequent serious adverse events (occurring in more than 10 patients) are listed in the Table 14 below:

Table 14: Most Frequent Serious Adverse Events in FAERS, September 1, 2016 - June 30, 2017

System Organ Classification (SOC)	Preferred Term (PT)	N (%)
Blood and lymphatic system disorders	thrombocytopenia	11 (1.25%)
	eosinophilia	12 (1.36%)
General disorders and administration site conditions	pyrexia	19 (2.15%)
Investigations	blood creatinine increased	10 (1.13%)
Renal and urinary disorders	acute kidney injury	58 (6.58%)
Respiratory disorders	dyspnea	14 (1.59%)
Skin and subcutaneous tissue disorders	erythema	10 (1.13%)
	pruritus	14 (1.59%)
	drug rash with eosinophilia and systemic symptoms (DRESS)	16 (1.81%)
	rash	26 (2.95%)
Vascular disorders	hypotension	12 (1.36%)

The common adverse events that were reported in FAERS with a frequency >2% were acute kidney injury (6.58%), rash (3.76%) and pruritus (2.34%). The majority of reported serious adverse events were noted in the following system organ classes: skin and subcutaneous system disorders (19.27%), renal and urinary disorders (11.79%) and respiratory, thoracic and

mediastinal disorders (6.92%). These findings are in line with safety reports presented in the reviewed literature.

Reviewer's Comment: The reported common adverse events are labeled adverse reactions.

Safety findings from scientific publications identify the main adverse reactions of vancomycin as follows:

- nephrotoxicity (e.g., acute kidney injury, interstitial nephritis)
- ototoxicity
- infusion-related events (e.g., hypotension, red man syndrome)
- hematopoietic (neutropenia, thrombocytopenia)
- phlebitis
- chills, fever
- rashes

The overall evaluation of the literature and FAERS database has not identified any potential new safety signals with vancomycin use. Of note, the addition of PEG 400 and NADA as excipients contained in this formulation were found to have potential risks for embryo-fetal toxicity (please refer to the Pharmacology/Toxicology section of this review). In preclinical studies, teratogenic findings observed in rabbits and rats, resulted in some embryo-fetal findings including spinal malformations and ventricular septal defects with the excipients (PEG 400 and NADA). Additionally, the fixed dose strengths of 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL may exceed dosing requirements for younger pediatric populations.

Reviewer's Comment: The clinical reviewer concludes that the safety profile of Vancomycin Injection, without the excipients PEG 400 and NADA, is acceptable and that there are no new safety signals noted in the literature or in the FAERS data. However, the addition of PEG 400 and NADA excipients to this vancomycin formulation were found to have potential risks of embryo-fetal toxicity. The risk of embryo-fetal toxicity, use in pregnancy, (b) (4) are communicated in labeling.

9. 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.

10. Pediatrics

On May 21, 2018 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.

11. Labeling Recommendations

11.1. Prescribing Information (PI)

The following new labeling recommendations are based on the new nonclinical findings in the animal reproduction studies with the excipients polyethylene glycol (PEG 400) and N-acetyl-D-alanine (NADA), which caused fetal malformations in animal reproduction studies in this application (see Table 15 below):

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 15: Summary of High-level Labeling Changes

Summary of Significant Labeling Changes		
Section	Applicant's Proposed Labeling	Approved Labeling
HIGHLIGHTS OF PRESCRIBING INFORMATION	No Boxed Warning.	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.
<i>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.</i>		

Summary of Significant Labeling Changes		
1 INDICATIONS AND USAGE	The proposed indications were the same as the RLD including septicemia, infective endocarditis, skin and skin structure infections, bone infections, and lower respiratory tract infections.	- Septicemia - Infective endocarditis - Skin and skin structure infections - Bone Infections - Lower Respiratory Infections
<i>Reviewer's Comment: The treatment indications remained consistent with the RLD.</i>		
2. DOSAGE AND ADMINISTRATION 2.1 Important Administration Instructions 2.3 Dosage in Pediatric Patients with Normal Renal Function	(b) (4)	(b) (4) - This formulation of VANCOMYCIN Injection should be used only in patients who require the entire (500 mg, 1 g, 1.5 g or 2 g) dose and not any fraction thereof. - Use this formulation of Vancomycin Injection only in pediatric patients who require the entire dose (500 mg, 1 g, 1.5 g or 2 g) of this single-dose flexible bag and not any fraction of it.
<i>Reviewer's Comment. This new formulation for Vancomycin Injection is supplied in a single-dose flexible bag. Dosing for pediatric patients who cannot use the entire contents of the single-dose flexible bag is a safety concern including the potential for medication errors (i.e., overdosing) and risk of contamination with the unused portion of the single bag. To mitigate such potential safety risks, the Division proposed the labeling changes under Section 2. Dosage and Administration as noted in the table above.</i>		
3 DOSAGE FORMS AND STRENGTHS	The description did not provide adequate details regarding the four dosage strengths or that the flexible bags are supplied in sealed aluminum overpouches.	Additional information regarding the dosage strengths was provided and clarification that the flexible bags are supplied in sealed aluminum overpouches.

Summary of Significant Labeling Changes		
<i>Reviewer's Comment: Additional information regarding the dosage strengths and description of the flexible bags was provided for clarity.</i>		
5 WARNINGS AND PRECAUTIONS 5.1 Embryo-Fetal Toxicity Due to PEG 400 and NADA Excipients	No discussion of embryo-fetal toxicity.	- 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. - If use of vancomycin is needed during pregnancy, use other available formulation of vancomycin
<i>Reviewer's Comment: This formulation of 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.</i>		
8 USE IN SPECIFIC POPULATIONS	The Applicant drafted this section in PLLR format; however, did not emphasize that PEG 400 and NADA caused fetal malformations in animal reproduction studies.	Relevant subsections were revised based on the findings in the animal reproduction studies with the excipients PEG 400 and NADA, which caused fetal malformations.
<i>Reviewer's Comment: Revisions to the PLLR subsections were made based on input from DPMH and the Pharmacology/Toxicology review team.</i>		
16 HOW SUPPLIED/STORAGE AND HANDLING	Minimal information was provided.	Additional information was provided for the description of the product and packaging configuration.
<i>Reviewer's Comment: Revisions made to increase clarity regarding the description of the product and packaging configuration.</i>		

Summary of Significant Labeling Changes		
17 PATIENT COUNSELING INFORMATION	• This section was modeled after the RLD's label and did not contain counseling information related to the risk of embryo-fetal toxicity.	• Risk of Embryo-Fetal Toxicity: Advise patients to notify their healthcare provider if they are pregnant prior to treatment with this formulation of vancomycin.
<i>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.</i>		

11.2. Patient Labeling

Not applicable.

12. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

12.1. Safety Issue(s) that Warrant Consideration of a REMS

Not applicable.

12.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

12.3. Recommendations on REMS

Not applicable.

13. Postmarketing Requirements and Commitments

None.

14. Appendices

14.1. References

- (1) FDA Adverse Events Reporting System (FAERS)
- (2) Fiorito TM, Luther MK, Dennehy PH, LaPlante KL Matson KL Nephrotoxicity With Vancomycin in the Pediatric Population: A Systematic Review and Meta-Analysis. *Pediatr Infect Dis J*. 2018 Jul;37(7):654-661.
- (3) Lacave G, Caille V, Bruneel F, Palette C, Legriel S, Grimaldi D, Eurin M, Bedos JP Incidence and risk factors of acute kidney injury associated with continuous intravenous high-dose vancomycin in critically ill patients: A retrospective cohort study. *Medicine (Baltimore)*. 2017 Feb;96(7).
- (4) Rubinstein E, Keynan Y. Vancomycin revisited - 60 years later. *Front Public Health*. 2014 Oct 31;2:217
- (5) Luther MK, Timbrook TT et al. Vancomycin Plus Piperacillin-Tazobactam and Acute Kidney Injury in Adults: A Systematic Review and Meta-Analysis. *Crit Care Med*. 2018 Jan;46(1):12-20.
- (6) Witkin AJ, Chang DF, Jumper JM, et al. Vancomycin-associated hemorrhagic occlusive retinal vasculitis, *American Journal of Ophthalmology* 2017; 124(5):583-595
- (7) D'souza AD & Shegokar R Polyethylene glycol (PEG): a versatile polymer for pharmaceutical applications, *Expert Opinion on Drug Delivery*, 13:9, 1257-1275.
- (8) Centers for Disease Control and Prevention (CDC) Fact Sheet.
- (9) Baxter Vancomycin Injection prescribing information

14.2. Nonclinical Pharmacology/Toxicology

Table 16: Litter Incidence of Select Major Abnormalities in Embryo-Fetal Study of NADA in New Zealand White Rabbit with ^{(b) (4)} Historical Controls

NADA Embryo-fetal Rabbit Study		Treatment Group (mg/kg NADA IV)				2017 ^a	2017-18 ^b	All Data ^c
		Control	560	1680	3780	HCD	HCD	HCD
Dams Pregnant		23	23	23	5	-	-	-
Litters Aborted		2	1	0	2	-	-	-
Euthanized Early-Welfare Reason		0	0	1	1	-	-	-
Total Live Fetuses		159	171	165	13	1213	1712	2925
Litters in Group		21	22	22	2	154	219	373
Major Skeletal Abnormalities								
Cervical/Thoracic scoliosis	Fetal (%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Litter (%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lumbar Scoliosis	Fetal (%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	2 (0.2%)	1 (0.1%)	3 (0.1%)
	Litter (%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	2 (1.3%)	1 (0.5%)	3 (0.8%)
Total scoliosis	Fetal (%)	0 (0%)	0 (0%)	2 (1.2%)	0 (0%)	2 (0.2%)	1 (0.1%)	3 (0.1%)
	Litter (%)	0 (0%)	0 (0%)	2 (9.1%)	0 (0%)	2 (1.3%)	1 (0.5%)	3 (1.1%)
Multiple Vertebral/Rib Abnormalities	Fetal (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	3 (0.2%)	4 (0.1%)
	Litter (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	3 (1.4%)	4 (1.1%)
Total Major Vertebral Abnormalities	Fetal (%)	0 (0%)	0 (0%)	2 (1.2%)	0 (0%)	3 (0.2%)*	4 (0.2%)*	7 (0.2%)*
	Litter (%)	0 (0%)	0 (0%)	2 (9.1%)	0 (0%)	3 (1.9%)*	4 (1.8%)*	7 (1.9%)*
Major Cardiovascular Abnormalities								
Dilated Ascending aorta/aortic arch	Fetal (%)	0 (0%)	0 (0%)	2 (1.2%)	0 (0%)	3 (0.2%)	4 (0.2%)	7 (0.2%)
	Litter (%)	0 (0%)	0 (0%)	2 (9.1%)	0 (0%)	3 (1.9%)	4 (1.8%)	7 (1.9%)
Dorsally displaced pulmonary trunk	Fetal (%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)	2 (0.1%)	2 (0.1%)
	Litter (%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	2 (0.9%)	2 (0.3%)
Truncus arteriosus	Fetal (%)	0 (0%)	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)	1 (0.1%)	1 (0.03%)
	Litter (%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	1 (0.5%)	1 (0.3%)
Membranous ventricular septal defect	Fetal (%)	0 (0%)	0 (0%)	0 (0%)	1 (7.7%)	2 (0.2%)	1 (0.1%)	3 (0.1%)
	Litter (%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	2 (1.3%)	1 (0.5%)	3 (0.8%)
Muscular ventricular	Fetal (%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)	4 (0.2%)	4 (0.1%)

NADA Embryo-fetal Rabbit Study		Treatment Group (mg/kg NADA IV)				2017 ^a	2017-18 ^b	All Data ^c
septal defect	Litter (%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	4 (1.8%)	4 (1.1%)
Misshapen heart	Fetal (%)	0 (0%)	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)	2 (0.1%)	2 (0.1%)
	Litter (%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	2 (0.9%)	2 (0.5%)
Other Major Abnormalities								
Amelia	Fetal (%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Litter (%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Thoracogastroschisis	Fetal (%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Litter (%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

HCD= Historical Control Data. ^aHistorical control data from (b) (4) Laboratories of studies conducted with (b) (4) NZW from 2017. ^bHistorical control data from (b) (4) Laboratories of studies conducted with (b) (4) NZW from 2017- 2018. ^cHistorical control data from all submitted (b) (4) NZW from 2017-2018. *The indices for Total Major Vertebral Abnormalities in historical controls is the combination of the values for total scoliosis and multiple vertebral/rib abnormalities. It is likely the values for Total Major Vertebral Abnormalities in HCD are elevated.

Table 17: Litter Incidence of Select Major Abnormalities in EmbryoFetal Study of PEG 400 in New Zealand White Rabbit with (b) (4) Historical Controls

PEG 400 EmbryoFetal Rabbit Study		Treatment Group (mg/kg PEG 400 IV)				2013-2017 ^a	2016-2017 ^b	2013-2017 ^c
		Control	500	1000	2000	HCD	HCD	Total HCD
Dams Pregnant		20	20	19	22	-	313	-
Litters Aborted		2	0	1	0	-	2	-
Euthanized Early-Welfare Reason		1	0	0	0	-	-	-
Total Live Fetuses		124	169	161	190	1445	2850	4295
Litters in Group		17	20	18	22	152	308	460
Litters with Dead Fetuses		0 (0%)	0 (0%)	1 (0.6%)	2 (1.1%)	-	0 (0%)	-
Major Skeletal Abnormalities								
Cervical/Thoracic Scoliosis	Fetal (%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.5%)	1 (0.1%)	5 (0.2%)	6 (0.1%)
	Litter (%)	0 (0%)	0 (0%)	1 (5.6%)	1 (4.5%)	1 (0.7%)	5 (1.6%)	6 (1.3%)
Lumbar Scoliosis	Fetal (%)	1 (0.8%)	0 (0%)	0 (0%)	2 (1.0%)	0 (0%)	0 (0%)	0 (0%)
	Litter (%)	1 (5.9%)	0 (0%)	0 (0%)	2 (9.1%)	0 (0%)	0 (0%)	0 (0%)
Total Scoliosis	Fetal (%)	1 (0.8%)	0 (0%)	1 (0.6%)	3 (1.6%)	1 (0.1%)	5 (0.2%)	6 (0.1%)
	Litter (%)	1 (5.9%)	0 (0%)	1 (5.6%)	3 (13.6%)	1 (0.7%)	5 (1.6%)	6 (1.3%)
Multiple	Fetal (%)	2 (1.6%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	9 (0.3%)	9 (0.2%)

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PEG 400 EmbryoFetal Rabbit Study		Treatment Group (mg/kg PEG 400 IV)				2013-2017 ^a	2016-2017 ^b	2013-2017 ^c
Vertebral/Rib Abnormalities	Litter (%)	2 (11.8%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	8 (2.6%)	8 (1.7%)
Total Major Vertebral Abnormalities	Fetal (%)	3 (2.4%)	0 (0%)	1 (0.6%)	3 (1.6%)	1 (0.1%)	9 (0.3%)	9 (0.2%)
	Litter (%)	2 (11.8%)	0 (0%)	1 (5.6%)	3 (13.6%)	1 (0.7%)	8 (2.6%)	8 (1.7%)
Minor Skeletal Abnormalities								
Unossified cranial large anterior fontanelle	Fetal (%)	0 (0%)	1 (0.6%)	4 (2.5%)	3 (1.6%)	3 (0.2%)	-	-
	Litter (%)	0 (0%)	1 (5.0%)	3 (16.7%)	3 (13.6%)	3 (2.0%)	-	-
Unossified cranial large posterior fontanelle	Fetal (%)	0 (0%)	1 (0.6%)	3 (1.9%)	2 (1.0)	8 (0.6%)	-	-
	Litter (%)	0 (0%)	1 (5.0%)	3 (16.7%)	2 (9.1%)	6 (3.9%)	-	-
Delayed ossification of pubes	Fetal (%)	2 (1.6%)	9 (5.3%)	12 (7.4%)	11 (5.8%)	12 (0.8%)	-	-
	Litter (%)	2 (11.8%)	4 (20.0%)	3 (16.7%)	7 (31.8%)	8 (5.3%)	-	-
Delayed ossification of epiphyses	Fetal (%)	4 (3.2%)	2 (1.2%)	12 (7.4%)	11 (5.8%)	72 (5.0%)	-	-
	Litter (%)	3 (17.6%)	2 (10.0%)	3 (16.7%)	6 (27.3%)	36 (23.7%)	-	-
Delayed ossification of talus	Fetal (%)	2 (1.6%)	2 (1.2%)	8 (5.0%)	8 (4.2%)	5 (0.3%)	-	-
	Litter (%)	2 (11.8%)	2 (10.0%)	3 (16.7%)	5 (22.7%)	4 (2.6%)	-	-

^aHistorical control data from (b) (4) Laboratories of studies conducted with (b) (4) NZW from 2013-2017.

^bHistorical control data of studies conducted with (b) (4) NZW in database from 2016-2017 sent to Agency on 11/14/2018. ^cHistorical control data from all (b) (4) NZW datasets from 2013-2017. Due to the way the data was presented, litter incidence for the (b) (4) NZW historical controls and total historical control data may be elevated as it was difficult to distinguish which fetuses came from which litters. – indicates that the data was not provided.

14.3. OCP Appendices (Technical documents supporting OCP recommendations)

None.

15. Division Director (Clinical)

Concur with review.

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/

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