CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208910Orig1s000

CLINICAL REVIEW(S)

NDA 208910 SD1 Oral Vancomycin for Solution Kit

Clinical Addendum

Financial Disclosure

In Module 1.3.4 of the eCTD, the Applicant submits Form 3454, Certification: Financial Interests and Arrangements of Clinical Investigators.

The Sponsor reports no financial arrangements with any clinical investigators. No clinical studies were submitted to this NDA application.

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/s/

SHERAL S PATEL
01/10/2018

Clinical 505(b)(2) Review

Date	October 31, 2017
Subject	Clinical Review
NDA	208910
Applicant	RxM™ Therapeutics, LLC (A Wholly Owned Subsidiary of CutisPharma, Inc.)
Date of Submission	28 July 2017
PDUFA Goal Date	28 January 2018
Regulatory Pathway	505(b)(2)
Proprietary Name	Firvanq®
Established (USAN) names	Vancomycin Hydrochloride Powder for Oral Solution Kit
Dosage forms / Strength	When reconstituted, the resulting Vancomycin Hydrochloride Oral Solution contains the equivalent to either 25 mg/mL or 50 mg/mL of vancomycin in a Grape-Flavored Diluent
Proposed Indication(s)	1. Treatment of *C. difficile*-associated diarrhea 2. Treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin resistant strains)
Clinical Reviewer	Sheral S. Patel, M.D. (DAIP/OAP/OND/CDER)
Acting Clinical Team Leader	Dmitri Iarikov, M.D., Ph.D. (DAIP/OAP/OND/CDER)
Recommended:	Approval

1. Introduction

1.1 Drug

Vancomycin Hydrochloride Powder for Oral Solution Kit (Firvanq™) consists of (b) (4) vancomycin hydrochloride USP powder and pre-measured amounts of Grape-Flavored Diluent, in two separate containers, to be reconstituted by a pharmacist. The Vancomycin Hydrochloride Oral Solution contains the equivalent to either 25 mg/mL or 50 mg/mL of vancomycin in a Grape-Flavored Diluent for oral administration. The final drug product is available in five kit configurations as outlined in **Appendix 1**.

Reviewer comment: *This product may provide benefit by potentially reducing dosage errors of oral administration of vancomycin hydrochloride solution in patients who are unable to swallow capsules.*

1.2 Proposed Indications

The Applicant proposes two indications for their drug:

1. Treatment of *C. difficile* associated with diarrhea
2. Treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains)

1.3 Proposed Dosing Regimen

The proposed dosing regimen is summarized in Table **1.3-1**.

Table 1.3-1 Proposed dosing regimen for Vancomycin Hydrochloride Powder for Oral Solution Kit.

Indication	**Adults (≥18 years old)**	**Pediatrics (<18 years old)**
C. difficile-associated diarrhea	125 mg orally 4 times daily for 10 days.	40 mg/kg in 3 or 4 divided doses for 7 to 10 days. Total daily dosage should not exceed 2 g.
Enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains)	Total daily dosage is 500 mg to 2 g administered orally in 3 or 4 divided doses for 7 to 10 days.	

1.4 Regulatory Approval Pathway

The Applicant is pursuing the 505(b)(2) NDA regulatory pathway for approval of the proposed Vancomycin Hydrochloride Powder for Oral Solution Kit. Based on prior Agency agreements, the Applicant is relying on FDA's findings of safety and effectiveness of the listed vancomycin products for oral administration [Vancocin® Capsules (NDA 050606) and Vancomycin Hydrochloride Injection, powder, lyophilized for solution, (Hospira, Inc. ANDA 062911)] (**Appendix 2**).

1.5 Qualified Infectious Diseases Product (QIDP) Designation

On 24 February 2017, the Applicant was granted QIDP Designation of Vancomycin Hydrochloride, Powder for Oral Solution, 25 mg/mL and 50 mg/mL, for treatment of *Clostridium difficile* associated diarrhea.

1.6 Fast Track Designation

On 24 August 2017, the Applicant was granted Fast Track Designation of Vancomycin Hydrochloride, Powder for Oral Solution, 25 mg/mL and 50 mg/mL, for treatment of *Clostridium difficile* associated diarrhea.

1.7 Pediatric Research Equity Act (PREA) Waiver

On 13 October 2015, the Agency informed the Applicant that the statutory requirements of PREA do not apply to the proposed NDA.

1.8 Waiver of in vivo Bioavailability Studies

The Applicant requests a waiver from providing evidence of *in vivo* bioequivalence of Vancomycin Hydrochloride Powder for Oral Solution Kit relative to the reference drugs, Vancomycin Hydrochloride Capsules USP (NDA 050606) or Vancomycin Hydrochloride for Injection USP (NDA 050671) [Vancomycin Hydrochloride for Injection USP (ANDA 062911), which was approved based on NDA 050671, is the reference standard for these studies].

Based on prior agreements from 13 May 2015 Type B pre-IND meeting, the Applicant proposes to bridge efficacy of the Vancomycin Hydrochloride Power for Oral Solution Kit and Vancocin® Capsules (NDA 050606), provided all data meet the proposed acceptance criteria, from the following studies evaluating:

1. Solubility
2. Permeability
3. Dissolution
4. Minimum inhibitory concentration

1.9 Scope of Review

Because no new safety or efficacy studies were submitted to support this application, the clinical review is limited to the following: summary of prior Agency agreements, review of Applicant submitted post-marketing information, and labeling recommendations from the Clinical perspective. The crux of the review of the proposed product relies on findings from the Biopharmaceutics and Product Quality (CMC) teams.

2. Background

2.1 Commercial Availability

The Vancomycin Hydrochloride Powder for Oral Solution Kit is currently commercially available as Vancomycin in FIRST® Grape Solution Compounding Kit http://cutispharma.com/products/oral-solutions-suspension/vancomycin/ (*accessed 29 August 2017*). A video demonstrating how the components are to be mixed is available on the website at https://youtu.be/s9cs9d2nfZs (*accessed 29 August 2017*).

The Applicant also sells similar kits for baclofen, metronidazole, omeprazole, lansoprazole, mouthwash 'BLM' (Diphenhydramine HCl, Lidocaine HCl, Aluminum Hydroxide, Magnesium Hydroxide and Simethicone). Throughout prior interactions with the Applicant, the Agency was aware that the Vancomycin Hydrochloride Powder for Oral Solution Kit is commercially available.

2.2 Regulatory History

Vancomycin hydrochloride was first approved in the oral solution form. However, the oral solution formulation was subsequently withdrawn from the market, and now only the capsule and intravenous dosage forms are currently available in the United States (**Table 2.2-1**).

Reviewer comment: *Intravenous vancomycin formulations are frequently mixed with sweetening agents and administered orally, particularly in patients who cannot swallow capsules or when Vancocin® capsules are cost-prohibitive.*

Table 2.2-1 Orally administered vancomycin hydrochloride solution products

	Vancomycin hydrochloride Formulation	**NDA/ ANDA**	**Notes**
1	Oral capsules	NDA 50606	Approved in 1986.
2	Oral solution	ANDA 60667	Approved in 1972, manufacture stopped 2002.
3	Oral solution	ANDA 63321	Approved in 1993, withdrawn in 2007.
4	Injection, powder lyophilized, for solution	ANDA 62911, and multiple others	Oral administration in INDICATIONS and DOSAGE AND ADMINISTRATION sections of the label.

The Applicant, Cutis Pharma, Inc., previously submitted briefing documents for a potential NDA application for Vancomycin Hydrochloride Powder for Oral Solution Kit (i.e., PIND 123456 SD1, 2, 4, 7 and 10). Numerous complicated regulatory issues were raised during the review of these submissions.

In addition to all review disciplines within the Division of Anti-Infective Products, numerous Offices and Divisions within the Agency contributed to prior reviews for PIND 123456. This includes Biopharmaceutics, Product Quality Microbiology, Office of Compliance, Office of Generic Drugs, Office of Regulatory Policy, Office of Chief Counsel and the Division of Pediatrics and Maternal Health.

Please refer to the individual reviews and communications to the Applicant for details on the evolving thinking of the Agency regarding a proposed regulatory pathway for approval. Key regulatory interactions with the Applicant are summarized in **Appendix 3**.

Highlights of important points communicated to the Applicant regarding a potential NDA submission follow.

1. The Sponsor can rely on safety and efficacy data for the listed drugs Vancocin® (NDA 050606) and vancomycin hydrochloride for injection (ANDA 62911) for Agency approval. The Sponsor must establish a scientific bridge between the proposed Vancomycin Hydrochloride Powder for Oral Solution Kit and each listed drug.

2. For the scientific bridge to ANDA 62911, the Sponsor may request a biowaiver. The Sponsor must provide data from published literature and *in vitro* activity testing in order to support this biowaiver request.

3. For the scientific bridge to NDA 050606, the Sponsor must provide a scientific justification demonstrating the appropriateness of relying on that NDA for approval of the Vancomycin Hydrochloride Powder for Oral Solution Kit.

4. The Agency agreed that fulfillment of all of the aforementioned steps may constitute an alternate pathway to filing the NDA for Vancomycin Hydrochloride Powder for Oral Solution Kit. With this alternative regulatory approach, there would be no *in vivo* clinical trial (i.e., bioequivalency, noninferiority, or pharmacokinetic) study requirement for filing the NDA.

5. No additional nonclinical studies will likely be required as long as the impurity and degradant profile of your product meets or exceeds specifications for the RLD, and the detected amounts of each impurity or degradant in the stability studies with the final

formulation does not exceed levels approved in the RLD. The final decision on the need for any additional nonclinical studies to support the safety of the product will be made at the time of submission of the 505(b)(2) NDA.

6. Caco-2 testing results can be used to confirm the equivalent permeability of vancomycin from approved vancomycin products for oral administration and the proposed vancomycin Hydrochloride Powder for Oral Solution Kit.

7. The proposed solubility, permeability, dissolution and activity studies will adequately bridge efficacy of the Vancomycin Hydrochloride Powder for Oral Solution Kit to approved vancomycin products for oral administration.

8. In vivo studies can be waived based on adequate in vitro data, which will be determined at the time of the NDA review.

9. The proposed scientific bridge is adequate to support a 505(b)(2) NDA. A final determination regarding the need for further studies, in vitro and clinical, will be a review issue.

10. Statutory requirements of the Pediatric Research Equity Act (PREA) do not apply to the Sponsor's currently proposed NDA (See **Section 10**).

11. Numerous CMC-related comments.

For additional details regarding prior regulatory interactions, please refer to the Clinical Review for the pre-NDA meeting (PIND 123456 SD10), relevant Meeting Minutes, and the Applicant's Summary Table 6.2 located in Module 1.2 within the Reviewer's Guide.

3. CMC/ BIOPHARMACEUTICS

Please refer to the relevant discipline reviews for details. The Biopharmaceutics review was conducted by Yang Zhao, PhD. Product Quality Reviews were led by Dorota Matecka, PhD and conducted by a team addressing Drug Product, Drug Substance, Quality Microbiology, Process and Facilities.

In order to support a waiver from providing evidence of *in vivo* bioequivalence of Vancomycin Hydrochloride Powder for Oral Solution Kit relative to the reference drugs, the Applicant conducted solubility, permeability, dissolution and minimum inhibitory concentration (MIC) studies. A summary of Applicant reported study results follow.

1. Solubility

The Applicant conducted aqueous solubility studies, and reports that, consistent with published studies, vancomycin hydrochloride is highly soluble with respect to the Biopharmaceutics Classification System (BCS) criteria in both pH-controlled buffers, as well as in water.

2. Permeability

The Applicant evaluated the permeability of vancomycin hydrochloride, by studying the bidirectional Caco-2 permeability of Vancomycin Hydrochloride Oral Solution (25 mg/mL).

Three different preparations of Vancomycin Hydrochloride Solution were used: Vancomycin Hydrochloride in Grape-Flavored Diluent (test sample), Vancomycin Hydrochloride Capsules USP (in sterile water for injection) (reference drug) and Vancomycin Hydrochloride for Injection USP (in sterile water for injection) (reference drug).

The Applicant reports that all three preparations exhibited low permeability per BCS classification.

3. Dissolution

The Applicant evaluated the dissolution behavior of three Vancomycin Hydrochloride dosage forms under various physiologically relevant (human gastrointestinal tract) conditions: Vancomycin Hydrochloride Oral Solution (test sample) was compared to Vancomycin Hydrochloride for Injection, USP (in sterile water for injection) (reference drug) and Vancomycin Hydrochloride Capsules USP, 250 mg (reference drug).

As expected, the Applicant reports Vancomycin Hydrochloride Oral Solution and Vancomycin Hydrochloride for Injection. USP (in sterile water for injection) demonstrated nearly complete dissolution in excess of (b) (4)0% dissolved in 15 minutes. in all three dissolution media, making them "very rapidly dissolving" per BCS definitions.

In addition, as expected, the Applicant reports that rates of release for the Vancomycin Hydrochloride Oral Solution and Vancomycin Hydrochloride for Injection, USP (in sterile water for injection) are much faster than those observed for Vancomycin Capsules USP, under all conditions. For Vancomycin Hydrochloride Capsules, USP,

the Applicant reports that a discriminating dissolution profile was observed in all three dissolution media with at least (b) (4)% dissolved at 30 to 45 minutes.

4. Minimum Inhibitory Concentration

The Applicant evaluated the minimum inhibitory concentration (MIC) of Vancomycin Oral Solution. The Applicant studied Vancomycin hydrochloride aged for 6 months at *25°C/60%RH*, reconstituted with Grape-Flavored Diluent (aged 6 months at *25°C/60%RH),* and tested for MIC at initial and 30 days (refrigerated) time points. The Applicant compared these samples to freshly reconstituted vancomycin hydrochloride solution using Vancomycin Hydrochloride for Injection, USP, Vancomycin Hydrochloride Capsules, USP and (b) (4) laboratory standard.

The Applicant tested samples in triplicate against 100 strains each of *Clostridium difficile* and *Staphylococcus aureus.* The Grape-Flavored Diluent (aged 6 months at *25°C/60%RH)* used for reconstituting was run as a negative control.

The Applicant found that MICs were similar for all strains and storage of reconstituted Vancomycin Hydrochloride Oral Solution for 30 days at refrigerated conditions did not affect its microbial activity.

4. Nonclinical Pharmacology/Toxicology

Please refer to the Nonclinical Pharmacology/ Toxicology review by Terry Miller, PhD.

5. Clinical Pharmacology/Biopharmaceutics

Please refer to the Clinical Pharmacology review by Xiaohui (Tracey) Wei, PhD and the Biopharmaceutics review by Yang Zhao, PhD.

6. Clinical Microbiology

Please refer to the Clinical Microbiology review by Kalavati Suvarna, PhD.

7. Clinical/Statistical- Efficacy

7.1 Studies for proposed indications

The Applicant seeks approval of Vancomycin Hydrochloride Powder for Oral Solution Kit for the treatment of: 1. *C. difficile*-associated diarrhea and 2. Enterocolitis caused by *Staphylococcus aureus* (including methicillin resistant strains). The Applicant is relying on safety and efficacy data for the listed drugs Vancocin® (NDA 050606) and vancomycin hydrochloride for injection (ANDA 62911). Because no new safety or efficacy studies were conducted, no statistical review of the proposed product was conducted. See filing review by Statistical Reviewer, Cheryl Dixon, PhD for details.

7.2 C. difficile-*associated diarrhea*

Oral vancomycin has been used for the treatment of *C. difficile*-associated diarrhea for greater than 45 years. Oral vancomycin has minimal oral absorption and high fecal concentration relative to the minimum inhibitory concentration (MIC) of *C. difficile*. Multiple international societies have reviewed the literature and published evidence-based guidelines with all concluding that oral administration of vancomycin hydrochloride can be used to treat *Clostridium difficile*-associated diarrhea (also known as *Clostridium difficile* infection or CDI).[1-5] Furthermore, oral administration of vancomycin hydrochloride is the regimen of choice for the treatment of severe, complicated CDI.[1] Finally, oral vancomycin is the preferred treatment of the second or later recurrence of CDI using a tapered and/or pulse regimen.[1]

The Applicant conducted a literature review of data from 1977 to 1979, the time prior to approval of Vancocin® Hydrochloride for Oral Solution (ANDA 061667). There were ten published references describing the use of vancomycin in the treatment of antibiotic-associated pseudomembranous colitis (PMC) produced by *C. difficile*. There was a total of 46 patients included in these reports. All the patients reported had a documented diagnosis of antibiotic-associated PMC and responded to therapy with oral vancomycin.[6-15] One case was reported in a 13 year old child.[8]

7.3 Enterocolitis caused by Staphylococcus aureus *(including methicillin resistant strains)*

The Applicant seeks an indication of enterocolitis caused by *Staphylococcus aureus* (including methicillin resistant strains) based on current labeling of the referenced products.

Reviewer comment: *FDA-approved labeling for listed vancomycin products for oral administration [Vancocin® Capsules (NDA 050606) and Vancomycin Hydrochloride Injection, powder, lyophilized for solution, (Hospira, Inc.; ANDA 062911)] allows for two indications, 1. Treatment of C. difficile-associated diarrhea and, 2. Treatment of enterocolitis caused by Staphylococcus aureus (including methicillin-resistant strains).*

Inclusion of the second indication, treatment of enterocolitis caused by S. aureus requires further discussion. It should be noted that Section 14 CLINICAL STUDIES for Vancocin® Capsules, only provides information on treatment of C. difficile-associated diarrhea. No clinical data is provided in the Vancocin® Capsules label to support the S. aureus enterocolitis indication. The label for Vancomycin Hydrochloride for Injection, USP has not been converted per Physicians Labeling Rule, and there is no Section 14 in the current labeling. Since the Applicant is relying on findings of efficacy and safety of two approved drugs, the currently approved indications may be appropriate; however, leadership and Regulatory input is needed as this may impact other vancomycin hydrochloride applications.

Orally administered vancomycin was historically used for treatment of Staphylococcal enterocolitis, considered a serious complication of antibiotic therapy.[16-19] Vancomycin was administered orally by dilution of 0.5 grams of the parenteral dosage form in 30 ml of saline solution or fruit juice depending on whether the drug was given by gavage or swallowed at six-hour intervals until the diarrhea resolved.[18]

A key clinical feature which may help differentiate staphylococcal enterocolitis from C. difficile-associated diarrhea is large-volume, cholera-like diarrhea.[20] A predominance of gram-positive cocci in clusters on gram stain of stool or biopsy specimens, as well as the isolation of S. aureus as the dominant or sole flora support the diagnosis.[20] However, it is possible that patients receiving oral vancomycin for presumed staphylococcal enterocolitis were in fact infected with Clostridium difficile, which may result in a similar clinical picture. In addition, conventional stool cultures may fail to identify C. difficile, and exposure to antibiotics may leave S. aureus, including methicillin-resistant strains, as the only identifiable pathogen.[21]

In the premature infant population, Staphylococcus aureus (including methicillin resistant strains) is thought to be one of many causes of necrotizing enterocolitis.[22] However, these infants are typically treated with intravenous vancomycin.

8. Safety

8.1 Well described safety profile

Oral vancomycin has been used to treat of *Clostridium difficile* infections (CDI) for more than 45 years (**Table 2.2-1**). The safety profile of oral vancomycin is well described. Systemic absorption of oral vancomycin is typically minimal, and most of the drug remains in the gastrointestinal tract.[23]

Current labeling for Vancocin® capsules includes the following Warning and Precautions: potential for systemic absorption, nephrotoxicity, ototoxicity, superinfection, and development of drug-resistant bacteria. In clinical trials, the most common adverse reactions associated with Vancocin® capsules (≥ 10%) were nausea, abdominal pain, and hypokalemia. Nephrotoxicity (e.g., reports of renal failure, renal impairment, blood creatinine increased) occurred in 5% of subjects treated with Vancocin® capsules. In clinical trials, the following adverse reactions were higher among subjects >65 years of age than in subjects ≤65 years: hypokalemia, urinary tract infection, peripheral edema, insomnia, constipation, anemia, depression, vomiting, and hypotension. Adverse reactions noted in post-marketing for Vancocin® capsules include ototoxicity, reversible neutropenia, thrombocytopenia, anaphylaxis, drug fever, chills, nausea, eosinophilia, rashes (including exfoliative dermatitis), Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis and anaphylactoid reactions.

Reviewer comment: *Note that the disease process for which oral vancomycin is used to treat, CDI, can also result in gastrointestinal signs and symptoms, similar to the most common adverse reactions noted in the Vancocin® capsules label.*

8.2 Systemic absorption of oral vancomycin

Systemic absorption of oral vancomycin is typically minimal.[23]

In patients with CDI, serum vancomycin levels attained after oral vancomycin administration are proportional to the extent of colonic inflammation, dose of drug used, and level of renal impairment.[24]

Adverse effects resulting from systemic absorption of oral vancomycin described in the literature are primarily case reports, and include red man syndrome[25, 26], maculopapular rash[23, 27], leukopenia[28], and encephalopathy[29].

8.3 Recent Published Studies

In response to an Agency information request dated 30 August 2017, the Applicant provides a summary of worldwide experience on the safety of vancomycin and summary of recent literature publications related to safety of vancomycin within the last two years.

The Applicant conducted a PubMed Search of clinical studies using oral vancomycin and published between January 2015 and August 2017. No new safety signals for oral or intravenous vancomycin were identified. See **Appendix 4** for summary table of studies by Clinical Reviewer.

8.4 Applicant Pharmacovigilance Database for FIRST® Vancomycin Compounding Kit

The Applicant has been selling the proposed drug as FIRST® Vancomycin in the United States since 2014. Between 2014 and September 15, 2017, a total of (b) (4) FIRST® Vancomycin Compounding Kits have been sold to pharmacists. A total of 10 adverse events have been reported to the Applicant, none of which were serious and/or unexpected. All adverse events were consistent with oral or intravenous vancomycin drug product labeling, or published literature (**Appendix 5**). None of the reported adverse events were related to any pregnancy, delivery or infant-related event.

The Applicant reports a total of 5 adverse events between 2014 and September 2017 published in *Reactions Weekly* (**Appendix 6**). No new safety signals for oral or intravenous vancomycin were identified.

8.5 Vancomycin Administered during Pregnancy and Lactation

Data on the use of orally administered vancomycin during pregnancy and lactation are minimal and consist of case reports.[30-32] However, the risk of toxicity is likely low as systemic absorption of orally administered vancomycin is typically minimal.[23]

There is more data with the use of intravenous vancomycin in the treatment of pregnant women. Multiple studies and case reports show that, although transplacental passage of intravenous vancomycin was noted in cord blood, intravenous vancomycin did not lead to

sensorineural hearing loss, nephrotoxicity, abnormal APGAR scores, allergic reactions, or congenital abnormalities in the exposed infants.[33-39]

There are scant data on the use of oral or intravenous vancomycin administration and lactation. Because oral vancomycin is typically minimally absorbed, the excretion of oral vancomycin would be expected to be minimal. There are reports of intravenous vancomycin and excretion into breast milk.[33] The effect on the nursing infant is unknown, however some authors suggest potential concerns of bowel flora alterations and allergic reactions.[40]

Reviewer comment: *This reviewer finds it acceptable to use orally administered vancomycin hydrochloride in pregnant and lactating women based on the available data and current standards of care. In fact, vancomycin (1 g IV every 12 hrs until delivery) is one recommended regimen for intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal (GBS) disease in neonates.[41] Furthermore, intravenous vancomycin is frequently used to treat neonatal sepsis caused by resistant bacterial pathogens in very low birth weight, low birth weight and term neonates.[42, 43]*

Vancomycin hydrochloride for injection and for oral solution (NDA 209481) is currently under review by another team. The Division of Anti-Infective Products (DAIP) consulted the Division of Pediatric and Maternal Health (DPMH) on 31 October 2016, to assist with reviewing the Pregnancy and Lactation subsections of labeling for NDA 2094481. Excerpts (verbatim) from the review by Leyla Sahin, MD dated 19 April 2017 (DARRTS Reference ID: 4086133) follow and may be applicable to this NDA (208910).

Pregnancy Summary

Available published data on vancomycin use in pregnancy during the second and third trimesters have not shown an association with adverse pregnancy related outcomes. There are no studies on the safety of vancomycin exposure during the first trimester therefore it is not possible to draw any conclusions on the risk of birth defects following exposure to vancomycin in pregnancy. In addition, there are no data on the risk of miscarriage following fetal exposure to vancomycin. DPMH recommends the addition of data from the published studies to the Pregnancy subsection of labeling, under the Human Data heading.

Lactation Summary

Available limited data based on a single case report showed that vancomycin was present at a low level in milk. A single milk level is not sufficient to inform the levels of vancomycin in milk. There is little systemic absorption of vancomycin following oral administration, therefore breastfeeding is not expected to result in exposure of the infant to the drug. DPMH recommends that the single case report not be added to labeling and that information regarding poor oral absorption be added. DPMH recommends that the following risk/benefit

statement be included under the Risk Summary heading: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for vancomycin and any potential adverse effects on the breastfed infant from vancomycin or from the underlying maternal condition.

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

8.6 Hemorrhagic Occlusive Retinal Vasculitis

Hemorrhagic Occlusive Retinal Vasculitis (HORV) was recently added to the WARNINGS section of the label of another vancomycin NDA (vancomycin injection, USP, NDA 50671 S-24, approved 29 September 2017) as requested by the Agency in a correspondence dated 31 August 2017.

The following is an excerpt (verbatim in italics) from the Clinical Review by Alma Davidson, M.D., dated 28 September 2017 (DARRTS Reference ID: 4158221).

> *Hemorrhagic occlusive retinal vasculitis (HORV) is a rare and potentially devastating disease that can occur after an otherwise uncomplicated cataract surgery. In a retrospective case series study by Witkin et al[44], 36 eyes from 23 patients were diagnosed with HORV associated with intracameral or intravitreal use of vancomycin for endophthalmitis prophylaxis. It is suggested or hypothesized that this condition may represent a delayed hypersensitivity reaction to vancomycin.[44, 45] Based on review of these serious cases of HORV, we recommend revisions to the "WARNINGS" section of the prescribing information for Vancomycin Injection to inform prescribers regarding this serious adverse reaction associated with an off-label use of this product. The following revisions to the "WARNINGS" section are recommended and were sent to the applicant as a supplement request on August 31, 2017:*
>
> *"**WARNINGS***
> ***Hemorrhagic Occlusive Retinal Vasculitis (HORV)***
> *Hemorrhagic occlusive retinal vasculitis, including permanent loss of vision, occurred in patients receiving intracameral or intravitreal administration of vancomycin during or after cataract surgery. The safety and efficacy of vancomycin administered by the intracameral or intravitreal route have not been established by adequate and well-controlled studies. Vancomycin is not indicated for prophylaxis of endophthalmitis."*

Reviewer comment: *From a Clinical perspective, HORV should be added to the WARNINGS section of the proposed label. Although the proposed product is intended to be administered orally, the active drug product (vancomycin hydrochloride, USP) is the same as what is used for intravenous injection. Currently, the vancomycin hydrochloride for injection, USP is commonly used for oral administration, and was also being used off-label for intracameral or intravitreal administration.*

9. Advisory Committee Meeting

No Advisory Committee Meeting was held for this product.

10. Pediatrics

Based on the Applicant's previously submitted briefing packages, the Agency determined that the statutory requirements of Pediatric Research Equity Act (PREA) do not apply to the Applicant's currently proposed NDA. This is because the proposed product does not represent a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, as these characteristics are covered by previously approved single-ingredient vancomycin products (See Letter to Applicant 13 October 2015). Therefore, the Applicant's proposed NDA does not need to address PREA.

11. Other Relevant Regulatory Issues

Relevant regulatory issues have been discussed in the prior sections of this review.

12. Labeling

Reviewer comment: *Please refer to the Action package for the final approved label incorporating input from all disciplines, Division leadership and Applicant negotiations.*

12.1 Reference Labels

The proposed U.S. Prescribing Information (USPI) for Vancomycin Hydrochloride Powder for Oral Solution Kit is adapted from the USPI of the FDA-approved labeling for the referenced listed drugs [Vancocin® Capsules (NDA 050606, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a078d9c2-f89c-4f9f-8ded-60ffb2983c3f) and Vancomycin Hydrochloride for Injection, USP (Hospira, Inc.; ANDA 062911, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=37592c56-6679-48f4-169f-3a00c2ab114e)]. The Applicant has added text specifically applicable to the proposed drug product, such as the product name and manufacturer information, and provided updates to

meet the current Physician Labeling Rule (PLR)/Pregnancy and Lactation Labeling Rule (PLLR) requirements.

12.2 Pediatric Indication Statement

Recently, the Division has moved to providing an age group in the Indications statement for labeling. The Applicant is relying on FDA findings of safety and efficacy, as well as the literature, to support their application. In the two products the Applicant intends to use, there is no statement regarding an age group in the Indications statement of the currently approved label. (b) (4) there is pediatric dosing in the referenced product labels.

(b) (4)

12.3 Indication for Enterocolitis caused by Staphylococcus aureus (including methicillin resistant strains)

The Applicant proposes the indication for Enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains), which is consistent with the labeling for Vancocin® Capsules (NDA 050606) and Vancomycin Hydrochloride Injection, powder, lyophilized for solution, (Hospira, Inc.; ANDA 062911)]. However, the Clinical Studies Section (14) of the proposed label, only provides clinical trial data for Diarrhea Associated with *Clostridium difficile.* Internal discussion will be required regarding inclusion of the *S. aureus* enterocolitis indication, as this will likely impact multiple vancomycin hydrochloride applications. Please see **Section 7.3** for additional details.

12.4 Pregnancy and Lactation Labeling Rule (PLLR)

In response to Agency information request dated 30 August 2017, the Applicant submitted a revised label in PLLR format. Please refer to comments from DPMH consult obtained for NDA 209481 and summarized in **Section 8.5** of this review.

12.5 Hemorrhagic Occlusive Retinal Vasculitis (HORV)

Please see **Section 8.6** of this review regarding Clinical reviewer recommendations of adding HORV to the WARNINGS section of the label.

13. Recommendations/Risk Benefit Assessment

From a Clinical perspective, Vancomycin Hydrochloride Powder for Oral Solution Kit (Firvanq™, NDA 208910) is recommended for Approval.

Per prior Agency agreements, no new safety and efficacy studies were submitted for this 505(b)(2) application. The Applicant is relying on safety and efficacy data for the listed drugs Vancocin® (NDA 050606) and vancomycin hydrochloride for injection (ANDA 62911) for Agency approval. This product may provide benefit by potentially reducing dosage errors of oral administration of vancomycin hydrochloride solution in patients who are unable to swallow capsules.

14. References

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Appendix 1: Vancomycin Hydrochloride Powder for Oral Solution Kit Configurations

Vancomycin[a] Concentration after Reconstitution	Volume (as Dispensed)	Vancomycin Hydrochloride USP Powder Component	Grape-Flavored Diluent for Reconstitution
25 mg/mL	150 mL (5 FL OZ)	3.8 g	147 mL
	300 mL (10 FL OZ)	7.7 g	295 mL
50 mg/mL	150 mL (5 FL OZ)	7.7 g	145 mL
	210 mL (7 FL OZ)	10.8 g	203 mL
	300 mL (10 FL OZ)	15.4 g	289 mL

[a] As free-base

Source: *NDA 208910, Module 2.2 Introduction to the Summary, Table 2.2-1.*

Appendix 2: Reference Listed Drugs and Comparison with Proposed Drug Product

Table 1: Information on the Referenced Drugs

Referenced Drugs:	Vancomycin Hydrochloride Capsule USP (RLD)	Vancomycin Hydrochloride for Injection USP (RS)	Vancomycin Hydrochloride for Injection USP (RLD)
USP/USAN Drug Name:	Vancomycin Hydrochloride	Vancomycin Hydrochloride	Vancomycin Hydrochloride
Proprietary Name:	Vancomycin Hydrochloride	Vancomycin Hydrochloride	Vancomycin Hydrochloride
Application Holder:	ANI Pharmaceuticals, Inc.	Hospira, Inc.	Baxter Healthcare Corporation
Application Number:	NDA 050606	ANDA 062911[a]	NDA 050671[a]
Dosage Form:	Capsule	Injectable	Injectable
Strength:	125 mg, 250 mg	500 mg per vial	500 mg/100 mL, 750 mg/150 mL
Exclusivity Entitlement:	N/A	N/A	N/A
Patent Expiration Date(s):	N/A	N/A	N/A
Rx or OTC:	Rx	Rx	Rx

N/A = Not applicable
RLD = Reference Listed Drug
RS = Reference Standard
[a] NDA 050671 is the RLD for ANDA 062911.

Source: *NDA 208910, Module 1.12.11 Basis for Submission Statement, Table 1.12.11-1.*

Table 2: Comparison of the Proposed Drug Product and Reference Listed Drugs

Product:	Proposed Drug Product	Reference Listed Drug	Reference Standard Drug
Product Name:	Vancomycin Hydrochloride Powder for Oral Solution Kit	Vancomycin Hydrochloride Capsules USP	Vancomycin Hydrochloride for Injection, USP
Active Ingredients(s):	Vancomycin hydrochloride	Vancomycin hydrochloride	Vancomycin hydrochloride
Route of Administration:	Oral	Oral	Intravenous
Dosage Form:	Powder for Oral Solution	Capsule	Powder for Injection
Strength:	25 mg/mL, 50 mg/mL	125 mg, 250 mg	500 mg per vial

N/A = Not applicable.

Source: *NDA 208910, Module 1.12.11 Basis for Submission Statement, Table 1.12.11-2.*

Appendix 3: Regulatory History and Meeting Agreements/ Discussions with FDA (PIND 123456)

Meeting/Communication Date	Meeting/Communication Type	Meeting Topic Agreements/Discussions
17 Sep 2014	Type B, pre-IND	FDA Preliminary Response to Meeting Questions (email dated 17 Sep 2014)
13 May 2015	Type B, pre-IND	Sponsor Meeting Minutes (submitted 09 Jun 2015) FDA Meeting Minutes dated 12 Jun 2015 (Reference ID: 3778924)[a]
13 Oct 2015	Type B, pre-IND	Advice/Information Request Letter dated 13 Oct 2015 (Reference ID: 3832324)
20 Dec 2016	Type B, pre-NDA	FDA Meeting Minutes dated 13 Jan 2017 (Reference ID: 4040777)
24 Feb 2017	Letter	Grant Qualified Infectious Disease Product Designation dated 24 Feb 2017 (Reference ID: 4060057)
24 May 2017	Type B, CMC, pre-NDA	Sponsor Meeting Minutes (submitted 01 Jun 2017) FDA Meeting Minutes dated 09 Jun 2017 (Reference ID: 4109431)

[a] FDA's Meeting Minutes include copies of FDA's revised preliminary response dated 04 Feb 2015, an email communication received from FDA on 22 Feb 2015 and FDA's preliminary responses to the revised questions sent to the Sponsor on 11 May 2015.

Source: *NDA 208910, Module 1.2 Reviewer's Guide, Table 6-1.*

Appendix 4: Summary of Clinical Studies Using Oral Vancomycin and Published Between January 2015 and August 2017

Source	Study description	Reported adverse events
Vickers *et al.* 2017[47]	Phase 2, randomized, double-blind, non-inferiority study of ridinilazole (n=50) and oral vancomycin 125 mg every 6 hours for 10 days (n=50) for the treatment of *Clostridium difficile* infection (CDI).	Treatment emergent adverse events (TEAE) in vancomycin group reported in 40 (80%) subjects. TEAEs in Gastrointestinal SOC 28 (56%) Nausea 9 (18%), Abdominal pain 10 (20%), Abdominal distention 5 (10%), Vomiting 8 (16%), Flatulence 2 (4%), Diarrhea 5 (10%). Two participants in the vancomycin group had serious adverse events considered to be related to study drug; one subject had moderate hematemesis (which lead to study drug discontinuation) and septic shock and another subject had elevated liver enzymes and diarrhea. There were 2 deaths in the vancomycin group, none of which were related to study drug.
Boix *et al.* 2017	Phase 3, randomized, double-blind trial of surotomycin (n = 305) vs. oral vancomycin, 125 mg every 6 hours for 10 days (n = 286) for the treatment of CDI.	158 (55.2%) in the vancomycin reported at least one adverse event TEAEs in Gastrointestinal SOC 64 (22.4%) Abdominal pain 6 (2.1%) Constipation 4 (1.4%) Nausea 22 (7.7%) Vomiting 10 (3.5%) Diarrhea 14 (4.9%) There were no serious adverse events, TEAEs leading to study drug discontinuation or deaths in the vancomycin group.
Rahimpour *et al.* 2016[48]	Triple-blinded, randomized, placebo-controlled trial of oral vancomycin, 125 mg every 6 hours for 12 weeks for the treatment of primary sclerosing cholangitis (n = 29).	There were no adverse effects related to vancomycin during the 12 weeks of the study.
Louie *et al.* 2015[49]	Double-blind, randomized, Phase 2 study evaluating cadazolid vs. oral vancomycin, 125 mg every 6	10 (45.5%) in the vancomycin reported at least one adverse event Headache 3 (13.6%)

Source	Study description	Reported adverse events
	hours for 10 days (n = 22) for the treatment of CDI (total n=84).	Dizziness 2 (9.1%) Dyspepsia 2 (9.1%) Rash 2 (9.1%) Pain in extremity 2 (9.1%) Vancomycin treatment was discontinued for one participant who developed leukocytosis on Day 5.
Lee *et al.* 2016[50]	Phase 2, randomized, controlled, double-blind study of surotomycin vs. oral vancomycin, 125 mg every 6 hours for 10 days (n=70) for the treatment of CDI (total n = 207).	Adverse events in vancomycin arm included: Abdominal pain 7 (10%) Clostridial infection 4 (5.7%) Flatulence 5 (7.1%) Dizziness 5 (7.1%) Urinary tract infection 5 (7.1%) Nausea 4 (5.7%) Diarrhea 3 (4.3%) Headache 3 (4.3%) Two participants discontinued vancomycin because of an adverse event and there were two study deaths in the vancomycin group.
Antoon *et al.* 2016[51]	Prospective, observational, pilot studying the systemic absorption and renal safety of oral vancomycin in 8 children (ages 2 to 18 years) with *Clostridium difficile* colitis.	No patients had detectable levels of serum vancomycin. No adverse renal outcomes attributed to oral vancomycin. No cases of "Red Man" syndrome were observed.
Bhansali *et al.* 2015[52]	Randomized, evaluator-blind, active-controlled trial of the safety and pharmacokinetics of LFF571 (n=46) vs. oral vancomycin (n=26) 125 mg every 6 hours for 10 days in adults with moderate CDI (total n = 72).	No adverse events were reported in persons receiving vancomycin. The majority of participants receiving vancomycin had serum drug levels below the lower limit of quantitation (0.91 µg/mL) and the highest vancomycin serum concentration demonstrated was 2.73 µg/mL (subtherapeutic range).

Source: Table created by Clinical Reviewer.

Appendix 5: FIRST® Vancomycin Compounding Kit Reported Adverse Events

Year	AE Report Number	Patient Name (Initials)	DOB or Age	Gender	Reported AE
2014	C14 066 AE	Not provided	55 years old	female	No AE was reported - unknown dose was given (potential overdose)
2015	C15 023 AE	Not provided	6 years old	male	Brown stains on teeth
2015	C15 051 AE	Not provided	76 years old	female	alopecia and tooth discoloration
2015	C15 055 AE	(b) (6)	87 years old	female	reoccurrence of diarrhea after stopping vancomycin
2015	C15 092 AE		Not provided	male	"yellowing" of teeth, patient recanted complaint
2017	C17 004 AE		(b) (6)	female	hair loss
2017	C17 024 AE		Not provided	female	headache and ankle swelling
2017	C17 038 AE	Not provided	67 years old	female	Allergic reaction (headache)
2017	C17 041 AE	Not provided	72 years old	female	Severe diarrhea
2017	C17 048 AE	(b) (6)	(b) (6)	female	Dizziness, stomachache/gas pain and nausea

AE: Adverse Event

Source: NDA 208910 SD4 Module 2.5.5 Clinical Overview – Overview of Safety, Table 2.5.5-1.

Appendix 6: Reactions Weekly Reported Adverse Events (2014 to 2017)

Report	Year	Gender	Age	AE	Comment
Boyd *et al.*	2014	male	63 years old	neutrophilic dermatitis	Patient has Cryptococcus difficile colitis. Patient had hemodialysis-dependent end-stage renal disease, chronic obstructive pulmonary disease, and coronary artery disease.
Choudhry *et al.*	2015	female	60 years old	linear IgA bullous dermatosis	Patient was morbidly obese with history of hypertension, Type 2 diabetes mellitus and was admitted for acute encephalopathy.
Parks *et al.*	2016	male	74 years old	antibiotic-associated hemorrhagic colitis (overgrowth of Klebsiella Oxytoca)	
Villeneuve-Tang *et al.*	2016	female	88 years old	linear IgA bullous dermatosis	Patient received IV vancomycin and oral vancomycin
Draganescu *et al.*	2017	male	69 years old	3 toxic megacolon cases (in a hospital from 2014 to 2016) with favorable evolution with treatment with vancomycin and metronidazole and just one case whose evolution was aggravated under this therapy	Patient has unknown concomitant chronic diseases.

Source: NDA 208910 SD4 Module 2.5.5 Clinical Overview – Overview of Safety, Table 2.5.5-2.

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