CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208910Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: ***Approval***

NDA 208910
Review # 1

Drug Name/Dosage Form	FIRVANQ™ (vancomycin hydrochloride) for Oral Solution Kit
Strength	3.75 g, 7.5 g, 10.5 g, or 15 g vancomycin per bottle
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	CutisPharma Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	July 28, 2017	All
Amendment (eCTD 004)	September 29, 2017	Drug Substance, Microbiology
Amendment (eCTD 005)	November 7, 2017	Drug Product, Process
Amendment (eCTD 006)	November 27, 2017	Drug Product
Amendment (eCTD 007)	November 30, 2017	Process
Amendment (eCTD 008)	December 22, 2017	Labeling

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Gene Holbert	Benjamin Stevens
Drug Product	Yong Wang	Balajee Shanmugam
Process	Christine Falabella	Arwa El Hagrasy
Microbiology	David Bateman	John Metcalfe
Facilities	Frank Wackes	Derek Smith
Biopharmaceutics	Yang Zhao	Elsbeth Chikhale
Environmental Assessment (EA)*	Yong Wang	Balajee Shanmugam
Laboratory (OTR)	Cindy Diem Ngo	Jason Rodriguez
Regulatory Business Process Manager	Luz Rivera	N/A
Application Technical Lead	Dorota Matecka	N/A

*EA addressed in the Drug Product Addendum (Memorandum)

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	November 13, 2017	*Review by Gene Holbert (Panorama)*
	Type II			Adequate	May 23, 2017	*Review by Rohit V. Tiwari (DARRTS)*

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
preIND	123456	*Preliminary Meeting Responses and Minutes in DARRTS*

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	*Complete*	*Acceptable - refer to drug product and pharm/tox reviews*		
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA, as amended, has provided sufficient chemistry, Manufacturing and controls (CMC) information to assure the identity, strength, purity, and quality of the proposed drug product, vancomycin for oral solution. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was made in Panorama by the Office of Process and Facilities (OPF) on December 22, 2017. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. Summary of Quality Assessments

A. Product Overview

Vancomycin is a tricyclic glycopeptide antibacterial indicated for the treatment of a variety of infections such as:

- Serious or severe infections caused by susceptible isolates of methicillin-resistant staphylococci (MRSA)
- Septicemia
- Bone infections
- Lower respiratory tract infections
- Skin and skin structure infections
- Staphylococcal endocarditis
- *Clostridium difficile*- Associated Diarrhea
- Staphylococcal enterocolitis

The current NDA provides for vancomycin hydrochloride powder for oral solution to be used for the treatment of only two infections: 1) *Clostridium difficile* associated with diarrhea, and 2) Enterocolitis caused by *Staphylococcus aureus*. There are two listed drugs referenced in this 505(b)(2) NDA: 1) Vancocin® Capsules, 125 mg and 250 mg (NDA 50606) and Vancomycin Hydrochloride for Injection, 500 mg (ANDA 62911).

Proposed Indication(s) including Intended Patient Population	Treatment of: • *Clostridium difficile* associated with diarrhea; and • Enterocolitis caused by *Staphylococcus aureus* (including methicillin resistant strains) in adults and pediatric patients less than 18 years of age
Duration of Treatment	*Clostridium difficile* associated diarrhea: 10 days Staphylococcus enterocolitis: 7 to 10 days
Maximum Daily Dose	2 g (see the package insert for details)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

FIRNANQ (vancomycin hydrochloride) for Oral Solution Kit contains a bottle of (b) (4) vancomycin hydrochloride powder and a bottle of pre-measured Grape-Flavored Diluent to be used for vancomycin reconstitution by the pharmacist in order to provide a standardized, palatable oral solution (to be dispensed to the patient). When reconstituted, the product (vancomycin oral solution) contains the equivalent of either 25 mg/mL or 50 mg/mL of vancomycin (as outlined in the table below).

Vancomycin hydrochloride drug substance to be used in the proposed drug product is described as white, almost white or tan to brown powder freely soluble in water and insoluble in ether or chloroform. The CMC information for vancomycin hydrochloride drug substance has been provided via a reference to two DMFs Type II: (b) (4) held by (b) (4) and DMF (b) (4) held by (b) (4). DMF (b) (4) was reviewed in support of this application and found acceptable. In addition, DMF (b) (4) was previously found adequate in support of other applications in CDER. The retest period established for the vancomycin chloride drug substance stored between (b) (4) for is (b) (4) months.

The final drug product kits are supplied in the following vancomycin strength/diluent volume configurations (two right side columns):

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

The powder component of the kit includes only vancomycin hydrochloride with no other inactive ingredients. The diluent component contains the following excipients: artificial Grape Flavor (b) (4), D&C Yellow No. 10, FD&C Red No. 40, anhydrous citric acid, sucralose, purified water, and sodium benzoate (b) (4). All excipients are compendial, except for artificial Grape Flavor (b) (4), D&C Yellow No. 10, and FD&C Red No. 40. The two (b) (4), D&C Yellow No. 10 and FD&C Red No. 40, meet the requirements of 21 CFR 74.1710 and 21 CFR 74.1340, respectively, and therefore, are found acceptable. The information regarding Grape Flavor (b) (4) has been provided via a reference to a Type IV DMF. In addition, some information from a

supplier, including a product specification, was provided in the NDA and found acceptable by the drug product reviewer.

The specifications for both components of the kit, the vancomycin hydrochloride powder and the grape-flavored diluent, and for the reconstituted vancomycin solution include appropriate tests and acceptance criteria. During the NDA review several revisions to the listing of impurities, including any unspecified impurity, was implemented at the FDA recommendation. Also, several comments regarding the capabilities of the proposed analytical procedures, specifically, the HPLC procedures for impurities were addressed by the Applicant; in addition, non-compendial analytical procedures were identified by specific numbers in the proposed specifications. The proposed analytical procedures were verified and found by the FDA laboratory. The batch analyses data provided for a number of batches were found adequate to justify the proposed acceptance criteria in the drug product specifications.

The proposed container closure system for the finished drug product includes white oblong HDPE bottles (b) (4). Information provided in the NDA regarding the suitability of the proposed container closure system, including the information regarding the extractable and leachable profile, was found acceptable. Overall stability information provided in the NDA for the individual components of the drug product kit supports the proposed expiration dating of 24 months for the product to be stored at refrigerated conditions [2°C to 8°C (36°F to 46°F)]. In addition, based on the in-use stability data submitted in the NDA, the expiration dating of 14 days for the reconstituted vancomycin solutions to be stored at refrigerated conditions, has been found acceptable by the drug product reviewer.

The manufacturing process (b) (4)

(b) (4)

(b) (4)

Based on the overall information provided in the initial NDA submission and subsequent amendments, the proposed manufacturing process has been found acceptable.

No deficiencies were identified from the product quality microbiology perspective. The microbiology review focused on the description of the drug product composition, results of the (b) (4) effectiveness testing, description of the parameters to be used for the commercial production, the microbial limits test included in the proposed drug product specification (analytical procedure and acceptance criteria), results of the microbial limits testing performed on the registration batches, and information to support the preparation and storage recommendations for the reconstituted solution (for inclusion in the labeling). Consequently, the product quality microbiology information provided in the NDA was found acceptable.

The biopharmaceutics review focused on the review of the biowaiver request submitted by the Applicant to obtain a waiver from the requirement of conducting bioavailability/bioequivalence studies. Based on the information provided in the NDA, the biopharmaceutics reviewer concluded that a bridge between the proposed drug product [FIRVANQ™ (vancomycin hydrochloride) for Oral Solution Kit] and the listed drugs [Vancocin® Capsules, 125 mg and 250 mg (NDA 50606) and Vancomycin Hydrochloride for Injection, 500 mg (ANDA 62911)] has been established, justifying the reliance of this NDA on FDA's findings of safety and effectiveness of the listed vancomycin products for oral administration.

The vancomycin hydrochloride drug substance is manufactured by (b) (4) . The drug product is manufactured by RxM Therapeutics, LLC (a wholly owned subsidy of a Cutis Pharmaceuticals). Several other sites are involved in the release and stability testing of both drug substance and drug product. Based on the review of the application, inspectional history and results of the recent PAI inspection of the drug product facility, all facilities involved in the manufacture of the drug substance and drug product were found acceptable by the OPF reviewer. Consequently, the overall recommendation of "Approve" was entered for this NDA by OPF in Panorama on December 22, 2017.

B. Special Product Quality Labeling Recommendations (*refer to Labeling Chapter*)

C. Final Risk Assessment (*see Attachment I*)

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Process

CHAPTER IV: Microbiology

CHAPTER V: Biopharmaceutics

CHAPTER VI: Facilities

CHAPTER VII: Labeling

ATTACHMENT I: Risk Assessment

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MICROBIOLOGY

Product Background:

NDA: 208910

Drug Product Name / Strength: Vancomycin Hydrochloride/ 25 mg/mL and 50 mg/mL

Route of Administration: Powder for Oral Solution

Applicant Name: RxM™ Therapeutics, LLC (Wholly owned subsidiary of CutisPharma, Inc.)

Manufacturing Site:
Diluent: GCP Laboratories (GCP)
3600 25th Avenue, Gulfport, MS 39501

API and final oral solution kit:
CutisPharma, Inc.
841 Woburn St.
Wilmington, MA 01887

Method of Sterilization: None, Non-sterile drug product

Review Recommendation: Recommended for approval

Review Summary: (b) (4)

List Submissions being reviewed: July 28, 2017, and September 29, 2017.

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

Supporting/Related Documents: None

Remarks Section: This application was granted fast track review on August 24, 2017.

S Drug Substance

The drug substance will not be reviewed (b) (4).

P.1 Description of the Composition of the Drug Product

- Description of drug product:
  The drug product is comprised of a bottle containing the (b) (4) API, vancomycin hydrochloride powder and a separate grape flavored diluent as an oral solution kit. The pharmacy or hospital will reconstitute the kit, by adding the contents of the diluent to the API containing bottle prior to presenting the contents to the patient.

- Drug product composition:

Diluent

Ingredient	Content % (w/v)
Artificial grape flavor (b) (4),	(b) (4)
D&C Yellow No. 10	
FD&C Red No. 40	
Anhydrous citric acid, USP	
Sodium Benzoate, USP	
Sucralose, NF	
Purified water, USP	

API powder

Ingredient	25 mg/mL kit content per mL	50 mg/mL kit content per mL
Vancomycin hydrochloride, USP	(b) (4)	

- Description of container closure system:
  Diluent

Component	Description	Manufacturer
Bottle	(b) (4)	
Cap		

API:

Component	Description	Manufacturer
Bottle	(b) (4)	
Cap		

Reviewer's Assessment: Acceptable
The applicant provided an adequate description of the drug product composition and the container closure system.

P.2.5 Microbiological Attributes

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David Bateman

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John Metcalfe

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Date: 10/25/2017 02:16:39PM
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Comments: I concur with the primary reviewer's assessment.

BIOPHARMACEUTICS REVIEW

NDA: 208910

Drug Product Name/Strength: FIRVANQ™ (Vancomycin Hydrochloride) Powder for Oral Solution Kit (to be reconstituted with pre-measured Grape-Flavored Diluent to a solution with a vancomycin concentration of 25 mg/mL or 50 mg/mL)

Route of Administration: Oral

Applicant Name: CutisPharma Inc.

List Drugs (LDs): The Applicant has listed two LDs on Form 356h:
Vancomycin Hydrochloride Capsules USP, 125 mg and 250 mg **(NDA 50606)**
Vancomycin Hydrochloride for Injection USP, 500 mg **(ANDA 62911)**

Product Background:

Firvanq (Vancomycin Hydrochloride) Powder for Oral Solution Kit contains (b) (4) Vancomycin Hydrochloride powder USP which is co-packaged with pre-measured Grape-Flavored Diluent (5 different configurations, see details below) for reconstitution to a solution containing 25 mg/mL or 50 mg/mL of vancomycin. The packaged powder component contains no excipients and the diluent component contains (b) (4)% water and other excipients (artificial grape flavor (b) (4) D&C Yellow No. 10, FD&C Red No. 40, anhydrous citric acid, sodium benzoate, sucralose).

Vancomycin Hydrochloride Powder for Oral Solution Kit is proposed for the treatment of *C. difficile*-associated diarrhea and enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains). For the treatment of *C. difficile*-associated diarrhea, the suggested dose is 125 mg 4 times daily for 10 days in adult patients (≥ 18 years of age), and 40 mg/kg in 3 or 4 divided doses for 7 to 10 days with a total daily dosage not exceeding 2 g in pediatric patients (< 18 years of age). For the treatment of *S. aureus* enterocolitis, the suggested daily dose is 500 mg–2 g divided in 3 or 4 doses for 7 to 10 days in adult patients (≥ 18 years of age), and 40 mg/kg divided in 3 or 4 doses for 7 to 10 days with a total daily dosage not exceeding 2 g in pediatric patients (< 18 years of age).

Review Summary:

Submission: CutisPharma Inc. submitted NDA 208910 seeking approval for FIRVANQ™ (Vancomycin Hydrochloride) Powder for Oral Solution Kit under 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act.

Reviewer's Assessment: No safety or efficacy studies were submitted to support this application. The Applicant is relying on FDA's findings of safety and effectiveness of the listed vancomycin

products for oral administration [Vancocin® Capsules, 125 mg and 250 mg (NDA 50606) and Vancomycin Hydrochloride Injection, powder for solution, 500 mg (ANDA 62911)].

The Applicant requests a biowaiver for providing evidence of in vivo bioequivalence of Vancomycin Hydrochloride Powder for Oral Solution Kit relative to the above List Drugs. A waiver of the requirement to conduct in vivo bioavailability or bioequivalence studies under 21 CFR 320.22 is not applicable for the proposed drug product due to the different concentrations of vancomycin and excipients and different manufacturer compared to the List Drugs. However, per 21 CFR 320.24(b)(5) & (6), a bridge can be established between the proposed Vancomycin Hydrochloride Powder for Oral Solution Kit and each List Drug, because (1) Clinical safety and efficacy for oral Vancomycin administration have been demonstrated for the approved List Drugs; (2) The systemic bioavailability of Vancomycin after oral administration is very low/negligible and there is no expected difference between the negligible bioavailability of the proposed Vancomycin HCl Powder for Oral Solution Kit and the approved List Drugs; (3) The proposed drug product and the approved List Drugs are expected to reach similar efficacious Vancomycin concentrations in the colon at the site of action when the same drug amounts are given orally; (4) The proposed drug product and the List Drugs have similar in vitro activities (MICs) against *C.difficile* and *S. aureus*; (5) The Grape-Flavored Diluent does not have an in vitro activity against *C.difficile* or *S. aureus*; (6) The Grape-Flavored Diluent is not expected to alter the negligible bioavailability of Vancomycin.

Based on the provided information, a bridge between NDA 208910, FIRVANQ™ (Vancomycin Hydrochloride) Powder for Oral Solution Kit and the List Drugs of Vancomycin Hydrochloride Capsules and Vancomycin Hydrochloride for Injection is established, justifying the reliance of this NDA 208910 on FDA's findings of safety and effectiveness of the listed Vancomycin products for oral administration [Vancocin® Capsules, 125 mg and 250 mg (NDA 50606) and Vancomycin Hydrochloride Injection, powder for solution, 500 mg (ANDA 62911)].

Recommendation: From the Biopharmaceutics perspective, NDA 208910 for FIRVANQ™ (Vancomycin Hydrochloride) Powder for Oral Solution Kit is recommended for **APPROVAL**.

REVIEW:

1. Regulatory History:

Vancomycin Hydrochloride was first approved as an oral solution. However, the oral solution formulation was subsequently withdrawn from the market, and only the capsule and intravenous dosage forms are currently available in the United States (Table 1) (see Clinical Review by Sheral Patel dated November 1, 2017 in DARRTS).

Table 1. Orally administered Vancomycin Hydrochloride solution products

	Vancomycin HCl formulation	NDA/ANDA	Notes
1	Oral capsules	NDA 50606	Approved in 1986
2	Oral solution	ANDA 61667	Approved in 1972, stopped in 2002
3	Oral solution	ANDA 63321	Approved in 1993, withdrawn in 2007
4	Injection, powder lyophilized, for solution	ANDA 62911, NDA 50671 and multiple others	Can be administered orally per the INDICATIONS and DOSAGE AND ADMINISTRATION sections of the label

The List Drug, Vancocin® Capsules 125 mg and 250 mg (NDA 50606) is an immediate-release drug product, approved by the FDA on 4/15/1986. It contains (b) (4) API vancomycin hydrochloride, polyethylene glycol (b) (4). The approved dissolution acceptance criterion for Vancocin® Capsules is NLT (b) (4)% (Q) at 45 minutes.

The List Drug, Vancomycin Hydrochloride for Injection, 500 mg (ANDA 62911) is a lyophilized powder, supplied in vials used for preparing intravenous infusion, approved by the FDA on 8/4/1988. No clinical data were provided for ANDA 62911 at the time of approval. Per the approved label, the appropriate dose of Vancomycin Hydrochloride for Injection may be diluted in 1 oz (29.6 mL) of water and may be mixed with common flavoring syrups to improve the taste and given to the patients to drink. The reconstituted vancomycin concentration of the resulting solution is approximately 17 mg/mL.

In the current 505(b)(2) NDA (208910) submission, no safety or efficacy studies were submitted. Based on prior agreements made during the May 13, 2015 Type B pre-IND (IND-123456) meeting, the Applicant is relying on FDA's findings of safety and effectiveness of the above LDs [Vancocin® Capsules (NDA 50606) and Vancomycin Hydrochloride Injection (ANDA 62911, which is listed in the Orange Book as the Reference Standard)].

Originally, the Applicant planned (under IND-123456) to use only NDA 50606 as the LD, and proposed to conduct a Bioequivalence (BE) study with clinical end points between the proposed drug product and the LD of vancomycin capsules (NDA 50606). However, the Applicant was advised by FDA that an approved vancomycin oral solution or injection used as an oral solution can also be used as the LD, and that a biowaiver can be requested. Therefore, the Applicant decided to list both NDA 50606 for Vancomycin capsules and ANDA 62911 for Vancomycin for injection as the LDs, and to request a biowaiver instead of conducting a BE study between the proposed drug product and the Vancomycin capsules. Solubility, permeability, dissolution and in vitro activity (MIC) studies were conducted to support the bridge between the proposed drug product and the LDs.

2. Efficacy and Safety Information for Oral Vancomycin:

FDA-approved labeling for both LDs allows for two indications: 1. treatment of *C. difficile*-associated diarrhea and, 2. treatment of enterocolitis caused by *S. aureus* (including methicillin-resistant strains). The proposed Vancomycin Hydrochloride Powder for Oral Solution Kit also proposes these two indications, which is found acceptable by the Medical Officer (see Clinical Review by Sheral Patel dated November 1, 2017 in DARRTS).

3. Composition and Dosage of the Proposed Drug Product and the List Drugs:

The proposed Vancomycin Hydrochloride Powder for Oral Solution Kit is comprised of 39 [redacted] Vancomycin HCl Powder and pre-measured Grape-Flavored Diluent (containing artificial grape flavor [redacted] (b) (4) D&C Yellow No. 10, FD&C Red No. 40, anhydrous citric acid, sodium benzoate, sucralose, purified water) to be reconstituted by the pharmacist. The final drug product is available in five kit configurations (Table 2). When reconstituted, Vancomycin HCl oral solution contains the equivalent to either 25 mg/mL or 50 mg/mL of vancomycin in Grape-Flavored Diluent for oral administration. The Grape-Flavored Diluent has a composition of [redacted] (b) (4) % water and a pH between [redacted] (b) (4). A target pH range of [redacted] (b) (4) was observed in the final reconstituted solution of vancomycin HCl in Grape-Flavored Diluent.

Table 2. Vancomycin Hydrochloride Powder for Oral Solution Kit Configurations

Vancomycin Strength after Reconstitution	Volume (mL) (as dispensed)	Vancomycin HCl (g)	Grape-flavored diluent for reconstitution (mL)
50 mg/mL	300 (10 FL OZ)	[redacted] (b) (4) (equivalent to 15 g vancomycin)	289
50 mg/mL	210 (7 FL OZ)	[redacted] (b) (4) (equivalent to 10.5 g vancomycin)	203
50 mg/mL	150 (5 FL OZ)	[redacted] (b) (4) (equivalent to 7.5 g vancomycin)	145
25 mg/mL	300 (10 FL OZ)	[redacted] (b) (4) (equivalent to 7.5 g vancomycin)	295
25 mg/mL	150 (5 FL OZ)	[redacted] (b) (4) (equivalent to 3.75 g vancomycin)	147

The suggested doses of both the proposed drug product and the LDs for the treatment of *C. difficile*-associated diarrhea (125 mg 4 times daily for 10 days) or the treatment of *S. aureus* enterocolitis (500 mg–2 g divided in 3 or 4 doses for 7 to 10 days) in adult patients are the same. In pediatric patients (< 18 years of age), the suggested doses of both the proposed drug product and the LDs for the treatment of *C. difficile*-associated diarrhea and *S. aureus* enterocolitis is 40 mg/kg in 3 or 4 divided doses for 7 to 10 days.

4. Solubility:

The Applicant reported that Vancomycin HCl is highly soluble with respect to the BCS criteria in both pH-controlled buffers, as well as in water (Table 3).

Table 3. Applicant's provided Vancomycin solubility data in different pH aqueous buffers

Preparation No.	Concentration of Vancomycin as the Freebase (mg/mL)					
	pH 1	pH 3	pH 4	pH 5	pH 7.5	Water
1	295.5	161.6	10.2	7.7	21.6	128.9
2	298.1	172.4	10.1	8.0	21.6	129.7
3	343.4	163.5	9.9	7.9	17.0	135.9
Mean (3)	312.3	165.8	10.1	7.9	20.1	131.5
%-RSD	8.6	3.5	1.5	1.9	13.2	2.9

The Applicant reported that the vancomycin HCl solubility ranged from 130 – 170 mg/mL at 24.5 °C and 150 –170 mg/mL at 5 °C (Table 4).

Table 4. Applicant's provided Vancomycin API (Lot A4330001) solubility data in Grape-Flavored Diluent (Lot SGV005)

Storage [a]	mg/mL API[b]	pH	Notes
			(b) (4)

The solubility of Vancomycin HCl in the Grape-Flavored Diluent is significantly higher than the proposed highest drug product strength (50 mg/mL) at the proposed pH range of the drug product after reconstitution (b) (4) Therefore, the vancomycin is expected to be completely dissolved in the oral solution at 25 mg/mL or 50 mg/mL at 5 °C refrigeration and when stored at 24.5 °C room temperature. However, some gelling appears to occur at 5 °C refrigeration.

The CMC reviewer(s) will evaluate the vancomycin solubility and storage conditions, to ensure that the drug product is a true solution.

5. Permeability:

The Applicant provided bidirectional Caco-2 permeability data for the proposed Vancomycin HCl Oral Solution (VANCOMYCIN_(b) (4)) and the Vancomycin LDs at three pH levels (pH 5.7, 6.5, 7.4) using calibration curve quantitation. The data are expressed as apparent permeability (Papp): $Papp = \frac{dQ/dt}{C0A}$,

where dQ/dt is rate of permeation, C_0 is the initial concentration of test drug, and A is the area of monolayer (Table 5).

Table 5. Bidirectional Caco-2 permeability data for the proposed Vancomycin HCl Oral Solution (b) (4)) and the Vancomycin LDs (CAPSULE and LIQUID)

Test Article	pH	Mean A → B Papp 10^{-6} cm/s^{-1}	Mean B → A Papp 10^{-6} cm/s^{-1}	Efflux Ratio	Comments
VANCOMYCIN_(b) (4)_A4330001-6	5.7	< 0.1	< 0.1	NC	Low permeability
VANCOMYCIN_(b) (4)_A4330001-6	6.5	0.257	0.134	0.521	Low permeability
VANCOMYCIN_(b) (4)_A4330001-6	7.4	< 0.1	< 0.1	NC	Low permeability
VANCOMYCIN_CAPSULE_WF-002-005	5.7	< 0.1	< 0.1	NC	Low permeability
VANCOMYCIN_CAPSULE_WF-002-005	6.5	< 0.1	< 0.1	NC	Low permeability
VANCOMYCIN_CAPSULE_WF-002-005	7.4	< 0.1	< 0.1	NC	Low permeability
VANCOMYCIN_LIQUID_WF-002-006	5.7	< 0.1	< 0.1	NC	Low permeability
VANCOMYCIN_LIQUID_WF-002-006	6.5	< 0.1	< 0.1	NC	Low permeability
VANCOMYCIN_LIQUID_WF-002-006	7.4	< 0.1	< 0.1	NC	Low permeability
Metoprolol	7.4	9.58	27.2	2.85	High BCS control (class I BCS)
Ranitidine	7.4	0.067	1.57	27.7	Low perm. control (class III BCS)
Talinolol	7.4	0.027	4.00	226	P-gp Efflux control

NC: Not calculable.

Note: when concentrations for test articles in receiver well are below limit of quantitation (27 nM) this represents low permeability and corresponds to a Papp rate coefficient less than 0.1

Papp: apparent permeability rate coefficient

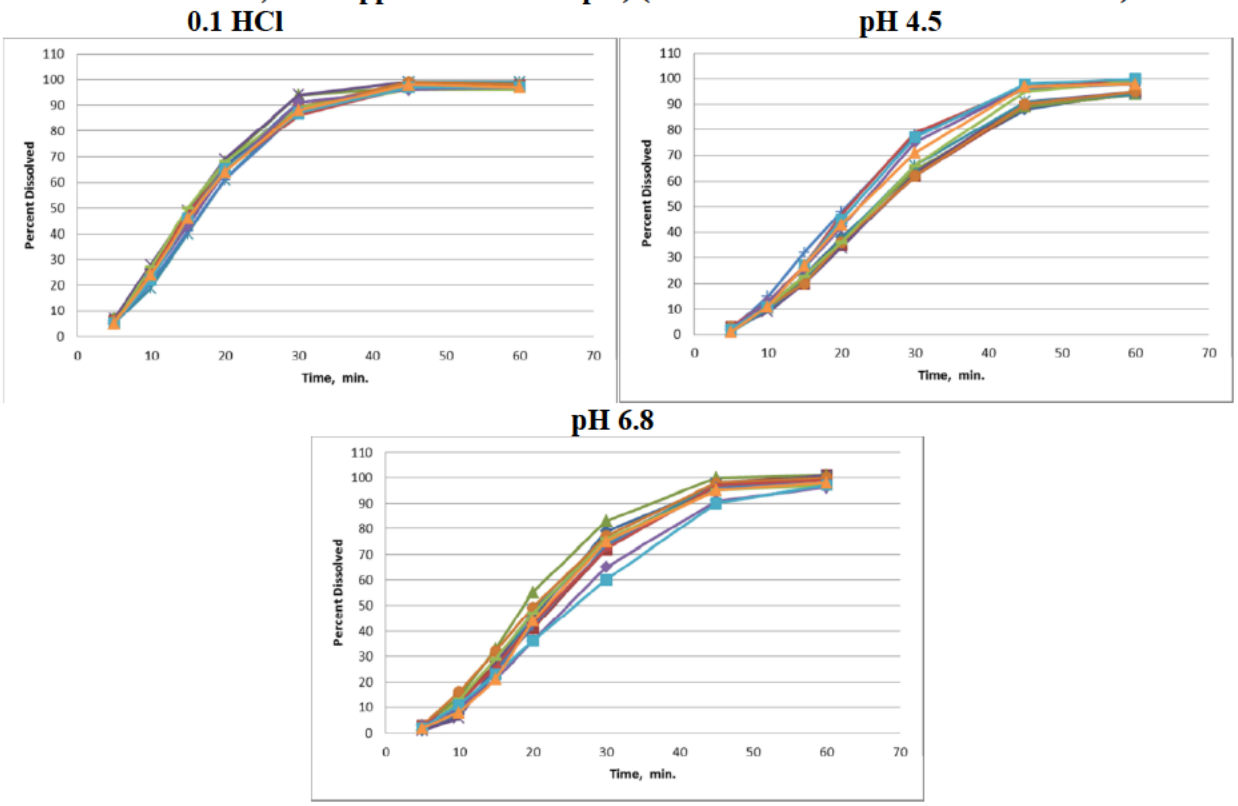
Efflux Ratio: P_{app} (B→A) / P_{app} (A→B)

Based on the provided data, Vancomycin exhibited low Caco-2 permeability for solutions prepared from the proposed drug product as well as the LD formulations and the presence of the Grape-Flavored Diluent in the proposed drug product did not significantly change the in vitro permeability of vancomycin. These observations are consistent with the labeling information for both the proposed and the LD products indicating that orally-administered vancomycin is poorly absorbed and that vancomycin concentrations in plasma and urine are generally undetectable following oral administration. Therefore, after oral administration, negligible systemic absorption of vancomycin is anticipated.

6. Dissolution:

Even though the drug is already in solution, the Applicant provided dissolution profiles for the proposed Vancomycin HCl Oral Solution and the Vancomycin injection LD in different dissolution media of 0.1 N HCl, pH 4.5, and pH 6.8 buffer (900 mL at 37 °C, USP Apparatus 2 at 50 rpm). As expected, the drug is completely (approximately 100%) dissolved at all time points. In addition, the Applicant provided dissolution profiles for Vancomycin Capsules which demonstrated more than 85% drug release in 30 minutes at pH 1.2, and more than 85% drug release in 45 minutes in pH 4.5 and 6.8 (Figure 1).

Figure 1. Dissolution for Vancocin® Capsules 250 mg in 0.1N HCl, pH 4.5, and pH 6.8 buffer (900 mL at 37 °C, USP Apparatus 2 at 50 rpm) (see APPENDIX for more information)



Based on the provided dissolution data, it is expected that Vancomycin from both the proposed drug product and the LD formulations can be completely solubilized to reach very similar concentrations in the environment of stomach/upper GI tract after oral administration of the same amount of Vancomycin.

7. Drug Concentrations at the Site of Action:

Per the FDA Draft Guidance on Vancomycin Hydrochloride (https://www.fda.gov/downloads/drugs/guidances /ucm082278.pdf), after oral administration of a vancomycin capsule, the drug is completely released in the stomach/upper GI tract, therefore, after taking the same amount of vancomycin from either the proposed drug product or the LDs, vancomycin concentrations are expected to reach very similar levels in the stomach/upper GI tract.

The vancomycin is expected to be completely solubilized in the GI fluid (whether given as a capsule or a solution). The completely solubilized vancomycin is then transported along with GI fluids to its site of action in the lower GI tract. In the lower GI tract at the site of action, the concentration of vancomycin is expected to be very similar whether given as the proposed drug product, or the LDs. The systemic concentrations of vancomycin after oral administration are expected to be negligible, whether given as the proposed drug product or the LDs.

8. Minimum Inhibitory Concentration (MIC):

The Applicant evaluated the minimum inhibitory concentration (MIC) of the proposed Vancomycin Oral Solution, an oral solution preparations from each LD, and a solution prepared from a vancomycin standard (obtained from (b) (4)), by testing samples in triplicate against 100 strains each of *C. difficile* and *S. aureus* with the Grape-Flavored Diluent run as a negative control. The Applicant stated that the in vitro activity of the reconstituted proposed drug product (RM-01, prepared from Vancomycin powder and Diluent stored for 6 months at 25 °C/60%RH) against *C. difficile and S. aureus* is almost identical to either an oral solution prepared from each LD, or a solution prepared from a vancomycin standard (obtained from (b) (4)). The Applicant also stated that the proposed drug product's activity against *C. difficile and S. aureus* does not decrease in potency when the reconstituted solution is stored for a period of 30 days at refrigerated temperature (Tables 6 and 7).

Table 6. In vitro activity (MIC, µg/ml) of various Vancomycin Hydrochloride formulations against *C. difficile*

	RM-01												(b) (4)		
	Time-0			30days			Capsules			IV					
Organism	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
C. difficile	1	1	1	2	1	1	2	1	1	2	1	2	1	1	1
C. difficile	2	2	1	2	1	1	2	2	2	2	1	2	1	1	1
C. difficile	1	1	1	1	1	1	1	2	1	2	2	1	1	1	1
C. difficile	2	1	1	1	2	1	2	1	2	2	1	2	1	1	1
Diluent control													Gr	Gr	Gr

Gr = growth

Table 7. In vitro activity (MIC, µg/ml) of various Vancomycin Hydrochloride formulations against *Staphylococcus aureus*

		RM-01 Time-0			RM-01 Time 30 days			Capsules			IV			(b) (4)		
Organism	Susc.	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
S.aureus	R	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1	0.5	0.5	0.5
S.aureus	R	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
S.aureus	S	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
S.aureus	S	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Diluent control														Gr	Gr	Gr

Gr = growth

9. Review of Biowaiver Request:

The Applicant requests a biowaiver for providing evidence of in vivo bioequivalence of Vancomycin Hydrochloride Powder for Oral Solution Kit relative to the LDs, Vancomycin Hydrochloride for Injection and Vancocin® Capsules (\\cdsesub1\evsprod\nda208910\0001\m1\us\112-other-correspondence\request-for-waiver-of-in-vivo-bioavailability-studies.pdf). A waiver of evidence of in vivo bioavailability or bioequivalence is not applicable for the proposed drug product under 21 CFR 320.22, due to the different concentrations of Vancomycin and excipients and different manufacturer compared to the List Drugs.

However, per 21 CFR 320.24(b)(5) & (6), a bridge can be established between the proposed Vancomycin Hydrochloride Powder for Oral Solution Kit and the List Drugs, because:

(i) Clinical safety and efficacy for oral Vancomycin administration have been demonstrated for the approved List Drugs. The proposed dosage for the proposed Vancomycin Hydrochloride Powder for Oral Solution Kit is the same as the approved dosage of the List Drugs.

(ii) Oral bioavailability of Vancomycin is very low/negligible and the drug is locally acting in the lower gastrointestinal (GI) tract. There is no difference expected in the negligible systemic availability of the proposed Vancomycin HCl Powder for Oral Solution Kit and the approved List Drugs after oral administration. This is supported by the Applicant's provided in vitro data showing that Vancomycin from the proposed drug product and the List Drugs exhibit low Caco-2 permeability.

(iii) For the treatment of *C. difficile*-associated diarrhea and *S. aureus* enterocolitis, vancomycin must be locally dissolved to be efficacious against the target microorganisms. Based on the solubility data, *in vitro* dissolution data and information from the FDA Draft Guidance on Vancomycin Hydrochloride (https://www.fda.gov/downloads/drugs/guidances/ucm082278.pdf), both the proposed drug product and the List Drugs are expected to offer similar vancomycin concentrations available at the site of action in the lower GI tract when the same amounts of vancomycin are given.

(iv) The proposed drug product and the List Drugs have similar in vitro activities (MICs) against 100 strains each of *C.difficile* and *S. aureus*.

(v) The Applicant has demonstrated that the Grape-Flavored Diluent does not have an in vitro activity against *C.difficile* or *S. aureus*.

(vi) The ingredients in the Grape-Flavored Diluent are listed in the FDA's Drug Database of Inactive Ingredients and are not expected to alter the negligible bioavailability of vancomycin.

Therefore, a bridge between the proposed Vancomycin Hydrochloride Powder for Oral Solution Kit and the approved List Drugs, Vancomycin Hydrochloride Capsules and Vancomycin Hydrochloride for Injection, is established, justifying the reliance of this NDA 208910 on FDA's findings of safety and effectiveness of the listed Vancomycin products for oral administration [Vancocin® Capsules, 125 mg and 250 mg (NDA 50606) and Vancomycin Hydrochloride Injection, powder for solution, 500 mg (ANDA 62911)].

REVIEWER'S RECOMMENDATIONS:

From a Biopharmaceutics perspective, NDA 208910 for the proposed Vancomycin Hydrochloride Powder for Oral Solution Kit is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer:
Yang Zhao, Ph.D. 11/29/2017
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Secondary Biopharmaceutics Reviewer:
I concur with Dr. Zhao's assessment.

Elsbeth Chikhale, Ph.D. 12/5/2017
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products/OPQ

APPENDIX

Table 8. Dissolution for Vancocin® Capsules 250 mg in 0.1N HCl, pH 4.5, and pH 6.8 buffer (900 mL, 37 °C, USP Apparatus 2 at 50 rpm)

	% Dissolved							% Dissolved							% Dissolved						
Vessel	5 min	10 min	15 min	20 min	30 min	45 min	60 min	5 min	10 min	15 min	20 min	30 min	45 min	60 min	5 min	10 min	15 min	20 min	30 min	45 min	60 min
	(b) (4)																				
Mean (12)	6	24	46	65	90	97	97	2	11	24	40	69	93	97	2	11	26	44	73	96	99
% RSD	13.7	10.7	6.7	3.9	2.9	1.2	0.9	33.1	13.7	15.8	12.3	9.7	4.1	2.4	38.5	27.8	15.0	12.2	8.2	3.0	1.8
Max	(b) (4)																				
Min																					

Yang Zhao

Digitally signed by Yang Zhao
Date: 12/05/2017 02:41:59PM
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Elsbeth Chikhale

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Date: 12/05/2017 03:11:58PM
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LABELING

IQA Review Guide Reference

NDA 208910

I. Package Insert

1. *Highlights of Prescribing Information*

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FIRVANQ™ (b) (4) safely and effectively. See full prescribing information for FIRVANQ (b) (4)

FIRVANQ™ (b) (4) (vancomycin hydrochloride) for oral solution
Initial U.S. Approval: 1964

DOSAGE FORMS AND STRENGTHS
Firvanq Kit contains: vancomycin, hydrochloride USP, powder for oral solution, equivalent to 3.75 g, 7.5 g, 10.5 g, or 15.0 g vancomycin and Grape-Flavored Diluent.

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	FIRVANQ™ vancomycin hydrochloride
Dosage form, route of administration	For Oral Solution
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	25 mg/mL or 50 mg/mL

2. *Section 2 Dosage and Administration*

2.4 Preparation and Storage of Firvanq (b) (4)

Firvanq Kit contains: 1 bottle of vancomycin hydrochloride USP powder and 1 bottle of pre measured Grape Flavored Diluent to be added to the vancomycin. A healthcare provider (i.e., a pharmacist), must reconstitute Vancomycin hydrochloride USP Powder with the Grape Flavored Diluent provided in the kit.

Firvanq (b) (4) is available in various strengths and volumes as shown in Table 1 (b) (4)

Vancomycin Concentration after Reconstitution	Final Volume of Firvanq after Reconstitution	Vancomycin Strength	Diluent for Firvanq
25 mg/mL	150 mL	3.75 g	147 mL
	300 mL	7.5 g	295 mL
50 mg/mL	150 mL	7.5 g	145 mL
	210 mL	10.5 g	203 mL
	300 mL	15 (b) (4) g	289 mL

Steps for the (b) (4) of Firvanq (b) (4)

1. Hold the neck of the bottle containing the vancomycin hydrochloride USP powder for oral solution (see Table 1 (b) (4)), and tap the bottom edges on a hard surface to loosen the powder.
2. Remove the cap from the bottle.
3. Tap the top of the induction seal liner to loosen any powder which may have adhered to the liner.
4. Carefully and slowly peel back the inner foil seal liner from the bottle.
5. Shake the Grape-Flavored Diluent (see table 1 (b) (4)) for a few seconds.
6. Open the diluent bottle and transfer about half the contents of the Grape Flavored Diluent into the vancomycin hydrochloride USP powder bottle.
7. Replace the cap and shake the vancomycin hydrochloride USP powder bottle vertically for approximately 45 seconds.
8. Add the remaining Grape Flavored Diluent into the vancomycin hydrochloride USP powder bottle.
9. Replace the cap and shake the bottle for approximately 30 seconds.
10. Instruct the patient to shake the reconstituted Firvanq solution well before each use and to use an oral dosing device that measures the appropriate volume of the oral solution in milliliters.

Storage of (b) (4) Firvanq (b) (4):

Store reconstituted Firvanq (b) (4) in the refrigerator, 2°C to 8°C (36°F to 46°F); discard the reconstituted solution after 14 days or if it appears hazy or contains particulates.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	1. Hold the neck of the bottle containing the vancomycin hydrochloride USP powder for oral solution (see Table 1 (b) (4)), and tap the bottom edges on a hard surface to loosen the powder. 2. Remove the cap from the bottle. 3. Tap the top of the induction seal liner to loosen any powder which may have adhered to the liner. 4. Carefully and slowly peel back the inner foil seal liner from the bottle. 5. Shake the Grape-Flavored Diluent (see table 1 (b) (4)) for a few seconds. 6. Open the diluent bottle and transfer about half the contents of the Grape Flavored Diluent into the vancomycin hydrochloride USP powder bottle. 7. Replace the cap and shake the vancomycin hydrochloride USP powder bottle vertically for approximately 45 seconds. 8. Add the remaining Grape Flavored Diluent into the vancomycin hydrochloride USP powder bottle. 9. Replace the cap and shake the bottle for approximately 30 seconds.

	10. Instruct the patient to shake the reconstituted Firvanq solution well before each use and to use an oral dosing device that measures the appropriate volume of the oral solution in milliliters. Storage of the (b) (4) Firvanq (b) (4) Store reconstituted Firvanq (b) (4) in the refrigerator at 2°C to 8°C (36°F to 46°F); discard the reconstituted solution after ***14*** days or if it appears hazy or contains particulates. (b) (4)

3. *Section 3 Dosage Forms and Strengths*

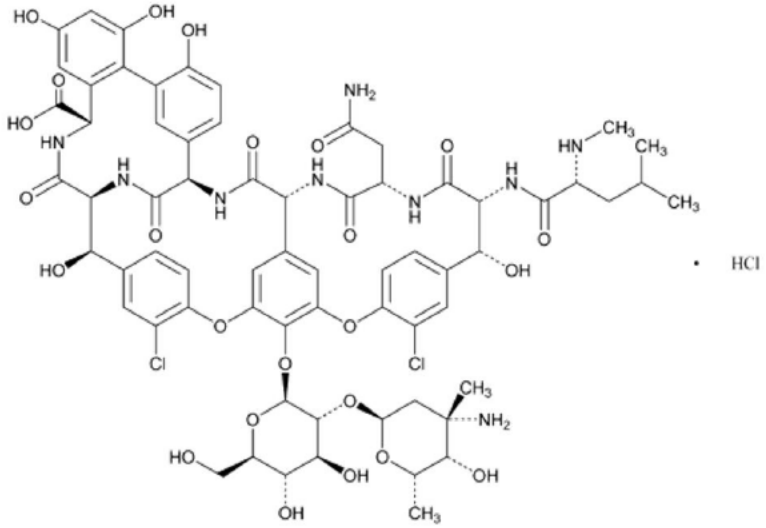
Each Firvanq Kit contains vancomycin hydrochloride USP as white to almost white or tan to brown powder for oral solution, equivalent to 3.75 g, 7.5 g, 10.5 g, or 15 (b) (4) g vancomycin, and Grape Flavored Diluent for reconstitution.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Oral solution
Strengths: in metric system	3.75 g, 7.5 g, 10.5 g, or 15 (b) (4) g vancomycin
Active moiety expression of strength with equivalence statement (if applicable)	equivalent to 3.75 g, 7.5 g, 10.5 g, or 15 (b) (4) g vancomycin,
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	as white to almost white or tan to brown powder for oral solution

4. *Section 11 Description*

Firvanq for oral administration contains hydrochloride salt of vancomycin, a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*), which has the chemical formula $C_{66}H_{75}Cl_2N_9O_{24}$•HCl. The molecular weight of vancomycin hydrochloride is 1485.71 g/mol.

Vancomycin hydrochloride has the structural formula:



Each Firvanq Kit contains a bottle of vancomycin hydrochloride, USP, as white to almost white or tan to brown powder for oral solution, and a bottle of pre-measured Grape Flavored Diluent, in the (b) (4) strengths:

Table 3: Vancomycin Strength, Diluent Volume and Vancomycin Concentration after Reconstitution

Vancomycin strength per bottle	Equivalent amount of vancomycin hydrochloride per bottle	Diluent for Firvanq	Vancomycin Concentration after Reconstitution
3.75 g	3.8 g	147 mL	25 mg/mL
7.5 g	7.7 g	295 mL	
7.5 g	7.7 g	145 mL	50 mg/mL
10.5 g	10.8 g	203 mL	
15.0 g	15.4 g	289 mL	

The Grape-Flavored Diluent used to reconstitute the oral solution contains: artificial grape flavor, citric acid (anhydrous), D&C Yellow No. 10, FD&C Red No. 40, purified water, sodium benzoate and sucralose.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Firvanq for oral administration contains hydrochloride salt of vancomycin
Dosage form and route of administration	Firvanq for oral administration
Active moiety expression of strength with equivalence statement (if applicable)	Refer to Table 3
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	NA
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	A tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*)
Chemical name, structural formula, molecular weight	Vancomycin hydrochloride $C_{66}H_{75}Cl_2N_9O_{24}$•HCl MW: 1485.71 g/mol
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	NA

5. *Section 16 How Supplied/Storage and Handling*

How Supplied

Each Firvanq kit contains a bottle of vancomycin hydrochloride USP, as white to almost white or tan to brown powder for oral solution, and a bottle of pre-measured Grape-Flavored Diluent, in the (b) (4) strengths and volumes, (b) (4)

Table 5: Vancomycin Strength, Diluent Volume and National Drug Code (NDC) Numbers

Vancomycin strength per bottle	Diluent for Firvanq	NDC Code
3.75 g	147 mL	65628-204-05
7.5 g	295 mL	65628-20(b)(4) 10
7.5 g	145 mL	65628-20 05
10.5 g	203 mL	65628-20 07
15 g	289 mL	65628-20 10

Storage and Handling

Store Firvanq prior to reconstitution at refrigerated conditions, 2°C to 8°C (36°F to 46°F).

Do not freeze. Keep container tightly closed. Protect from light.

Store reconstituted solutions of Firvanq at 2°C to 8°C *[see Dosage and Administration (2.4)]*.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Refer to Table 5
Available units (e.g., bottles of 100 tablets)	Each Kit
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	as white to almost white or tan to brown powder for oral solution, and a bottle of pre-measured Grape-Flavored Diluent
Special handling (e.g., protect from light)	Do not freeze. Keep container tightly closed. Protect from light.
Storage conditions	Store Firvanq prior to reconstitution at refrigerated conditions at 2°C to 8°C (36°F to 46°F). Store reconstituted solutions of Firvanq at 2°C to 8°C *[see Dosage and Administration (2.4)]*.
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: RM™ Therapeutics, LLC (A Wholly Owned Subsidiary of CutisPharma, Inc.) 841 Woburn St. Wilmington, MA 01887 USA

Reviewer's Assessment of Package Insert: *Adequate*

The information presented in the package insert is adequate from a CMC perspective. Note: the in-use period for the reconstituted solution should be no more than 14 days and should be discarded if any discoloration or haziness is observed within the 14 days.

{Assess if the Prescribing Information complies with all regulatory requirements from a CMC perspective}

- ***Any deficiencies should be listed at the end in the "List of Deficiencies"***

II. Labels:

1. ***Container and Carton Labels***

   For oral solution containing 25 mg/mL reconstituted with 147 ml Diluent

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Firvanq (b) (4) Vancomycin Hydrochloride To be consistent, use Vancomycin Hydrochloride (b) (4)	Firvanq (b) (4) Vancomycin Hydrochloride To be consistent, use Vancomycin Hydrochloride (b) (4)
Dosage strength	Vancomycin 25 mg/mL and When reconstituted, each mL contains: Vancomycin Hydrochloride, USP equivalent to 25 mg Vancomycin, USP OR Vancomycin 50 mg/mL and When reconstituted, each mL contains: Vancomycin Hydrochloride, USP equivalent to 50 mg Vancomycin, USP	Vancomycin 25 mg/mL in Grape Flavored Diluent or Vancomycin 50 mg/mL in Grape Flavored Diluent

Net contents	Not provided Delete (b) (4) and add the following statement: Before reconstitution, each bottle contains 3.75 g, 7.5 g, 10.5 g, or 15.0 g Vancomycin For diluent container label Delete (b) (4) Use the following DILUENT For reconstitution of 25 mg/mL Vancomycin for Oral Solution. Or DILUENT For reconstitution of 50 mg/mL Vancomycin for Oral Solution.	1 bottle containing Vancomycin Hydrochloride Powder equivalent to 3.75 g (b) (4) Vancomycin for oral solution 1 bottle containing 147 mL Grape Flavored Diluent for reconstitution When reconstituted, each mL contains 25 mg Vancomycin or 1 bottle containing Vancomycin Hydrochloride Powder equivalent to 7.5 g Vancomycin for oral solution 1 bottle containing 295 mL Grape Flavored Diluent for reconstitution When reconstituted, each mL contains 25 mg Vancomycin Or 1 bottle containing Vancomycin Hydrochloride Powder equivalent to 7.5 g Vancomycin for oral solution 1 bottle containing 145 mL Grape Flavored Diluent for reconstitution When reconstituted, each mL contains 50 mg Vancomycin Or 1 bottle containing Vancomycin Hydrochloride Powder equivalent to 10.5 g

		Vancomycin for oral solution 1 bottle containing 203 mL Grape Flavored Diluent for reconstitution When reconstituted, each mL contains 50 mg Vancomycin or 1 bottle containing Vancomycin Hydrochloride Powder equivalent to 15 g Vancomycin for oral solution 1 bottle containing 289 mL Grape Flavored Diluent for reconstitution When reconstituted, each mL contains 50 mg Vancomycin
"Rx only" displayed prominently on the main panel	Rx ONLY	Rx ONLY
NDC number (21 CFR 207.35(b)(3)(i))	Acceptable Note: the final dosage form is oral solution and the NDC is assigned to the kit which includes powder and vancomycin hydrochloride powder.	150 ml of 25 mg/ml: 65628-204-05 300 ml of 25 mg/ml: 65628-205-10 150 ml of 50 mg/ml: 65628-206-05 210 ml of 50 mg/ml: 65628-207-07 300 ml of 50 mg/ml: 65628-208-10
Lot number and expiration date (21 CFR 201.17)	Available for solution. Add lot number and expiration date for the diluent.	Available

Storage conditions	MUST BE REFRIGERATED Pharmacist: Use this bottle for dispensing after reconstitution, content must be used within 14 days. Use the following statement for the pharmacist. Pharmacist: Use this bottle for dispensing after reconstitution, content must be used within 14 days. Discard the product if it appears hazy or contains particulates.	Reconstitute before dispensing • For oral use only • Avoid contact with eyes • Keep container tightly closed • (b) (4) • Protect from light • Protect from freezing • Store kit at refrigerated temperature, 2°C-8°C, (36°F-46°F) [see USP] To the pharmacist: Important-prior to dispensing see package insert for complete instructions. When reconstituted each mL contains 25 mg (or 50 mg) vancomycin Instruct patient to store reconstituted formulation at refrigerated temperature, 2°C-8°C, (36°F-46°F) [see USP] Discard 14 days after reconstitution. To be consistent with the labeling, the following should be used: Discard 14 days after reconstitution or if it appears hazy or contains particulates.
Bar code (21CFR 201.25)	Available	Available

Name of manufacturer/distributor	CurtisPharma Wilmington, MA 01887 USA	CurtisPharma Wilmington, MA 01887 USA
And others, if space is available	Must be reconstituted before dispensing	For oral use only

Reviewer's Assessment of Labels: ***Adequate***

After review for the container labels for vancomycin oral solution and diluent and carton labels, the following should be communicated to the applicant:

1. In your container labels for Vancomycin Hydrochloride for oral solution, please update the following:

- Replace [redacted] (b) (4) with "vancomycin hydrochloride".
- Delete [redacted] (b) (4) and add "Each bottle contains vancomycin hydrochloride USP, powder for oral solution, equivalent to 3.75 g, 7.5 g, 10.5 g, or 15 g vancomycin".
- After "content must be used within 14 days", add "Discard the product if it appears hazy or contains particulates".

2. In the container labels for FIRVANQ Diluent, please update the following:

- Replace [redacted] (b) (4)" with "vancomycin hydrochloride".
- Indicate the space for lot number and expiration date
- Delete [redacted] (b) (4) and replace with "DILUENT for reconstitution of 25 mg/mL vancomycin for oral solution" or "DILUENT for reconstitution of 50 mg/mL vancomycin for oral solution".

3. In the carton labels, please update the following:

- Replace [redacted] (b) (4) with "vancomycin hydrochloride"
- Replace the statement [redacted] (b) (4) with "1 bottle containing Vancomycin Hydrochloride Powder equivalent to 3.75 g Vancomycin for oral solution" in one of the carton labels.
- Replace [redacted] (b) (4)" with "Discard 14 days after reconstitution or if it appears hazy or contains particulates".

{Assess if the labels comply with all regulatory requirements from a CMC perspective}

- ***Any deficiencies should be listed at the end in the "List of Deficiencies"***

List of Deficiencies:

1. In your container labels for Vancomycin Hydrochloride for oral solution, please update the following:
   - Replace [redacted] (b) (4)" with "vancomycin hydrochloride".
   - Delete "[redacted] (b) (4)" and add "Each bottle contains vancomycin hydrochloride USP, powder for oral solution, equivalent to 3.75 g, 7.5 g, 10.5 g, or 15 g vancomycin".
   - After "content must be used within 14 days", add "Discard the product if it appears hazy or contains particulates".

2. In the container labels for FIRVANQ Diluent, please update the following:
   - Replace [redacted] (b) (4) with "vancomycin hydrochloride".
   - Indicate the space for lot number and expiration date
   - Delete [redacted] (b) (4) and replace with "DILUENT for reconstitution of 25 mg/mL vancomycin for oral solution" or "DILUENT for reconstitution of 50 mg/mL vancomycin for oral solution".

3. In the carton labels, please update the following:
   - Replace [redacted] (b) (4)" with "vancomycin hydrochloride"
   - Replace the statement [redacted] (b) (4) [redacted]" with "1 bottle containing Vancomycin Hydrochloride Powder equivalent to 3.75 g Vancomycin for oral solution" in one of the carton labels.
   - Replace [redacted] (b) (4) with "Discard 14 days after reconstitution or if it appears hazy or contains particulates".

Overall Assessment and Recommendation:

From a CMC perspective, the proposed PI and labels for containers and cartons are acceptable upon resolving the above deficiencies.

Primary Labeling Reviewer Name and Date:

Yong Wang/January 16, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Yong Wang

Digitally signed by Yong Wang
Date: 1/18/2018 12:17:19PM
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Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 1/18/2018 02:27:42PM
GUID: 50758d5000003c1b1962e036ea11002c

ATTACHMENT I: Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay, stability of vancomycin	Formulation Raw materials Process parameters Scale/equipment Site	L	Adequate specification for the drug substance and drug product (b) (4)	Acceptable	
Uniformity of dose	Formulation Raw materials Process parameters Scale/equipment Site	L	Adequate (b) (4)	Acceptable	
Characteristics of reconstituted solution	Formulation Raw materials Process parameters Scale/equipment Site	M	Although some precipitation was observed in several in-use stability samples for some batches, no significant changes in other parameters (assay, pH, impurities, microbiological controls, etc.) over the proposed storage period (14 days for the reconstituted solution)	Acceptable	

Palatability	Formulation Raw materials Process parameters	M	Grape-flavored diluent	Acceptable	
Microbial limits	Formulation Raw materials Process parameters Scale/equipment Site	L	Adequate (b) (4) effectiveness testing results provided Microbial limits test included in release and shelf life DP specifications	Acceptable	
Leachables	Formulation Container closure system change	L	Adequate E/L data submitted Relatively short in-use storage time proposed	Acceptable	

NDA OVERALL RECOMMENDATION:

This NDA is recommended for **Approval** from the Product Quality perspective.

Dorota M.
Matecka -S

On behalf of OPQ Team
Dorota Matecka, Ph.D. ATL for NDA 208910