CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208910Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

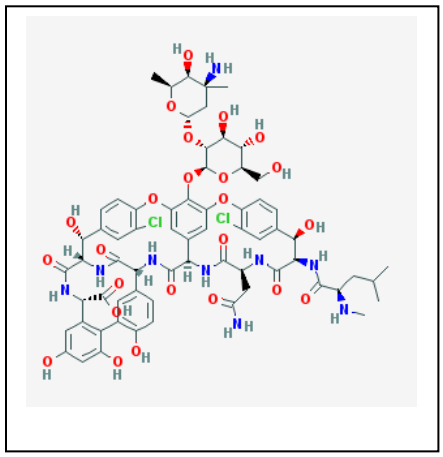
NDA # 208910

Date Company Submitted: 07/28/2017 to 09/29/2017
Date received by CDER: 07/28/2017 to 09/29/2017
Date Assigned: 07/31/2017
Date Completed: 11/17/2017
Reviewer: Kalavati Suvarna Ph.D.

NAME AND ADDRESS OF APPLICANT:
RxM™ Therapeutics, LLC (A Wholly Owned Subsidiary of CutisPharma, Inc.)
841 Woburn Street,
Wilmington, MA 01887

DRUG PRODUCT NAMES:
Proprietary Name: Firvanq®
Established Name: Vancomycin Hydrochloride
Chemical Name: (*Sa*)-(*3S,6R,7R,22R,23S,26S,36R,38aR*)-44-[[2-*O*-(3-Amino- 2,3,6-trideoxy-3-*C*-methyl-(-L-*lyxo*-hexopyranosyl)- (-D-glucopyranosyl]oxy]-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro- 7,22,28,30,32-pentahydroxy-6-[(*2R*)-4-methyl-2-(methylamino)]valeramido]-2,5,24,38,39-pentaoxo-*22H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-*1H,16H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid, monohydrochloride.

Structural formula:



Molecular weight: 1485.74
Empirical Formula: $C_{66}H_{75}Cl_2N_9O_{24}$. HCl

DRUG CATEGORY: Antibacterial

PROPOSED INDICATION:

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

PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT

Powder for Oral Solution Kit. The product contains (b) (4) vancomycin hydrochloride powder and pre-measured grape flavored diluent solution for reconstitution by the pharmacist. 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.

For *C. difficile* associated diarrhea (adults: 125 mg orally 4 times daily for 10 days; pediatric patients: 40 mg/kg in 3 or 4 divided doses for 7 to 10 days. The total daily dosage should not exceed 2 gm).

For Staphylococcal enterocolitis (adults: 500 mg to 2 gm orally in 3 or 4 divided doses for 7 to10 days; pediatric patients: 40 mg/kg in 3 or 4 divided doses for 7 to 10 days. The total daily dosage should not exceed 2 gm).

RELATED DOCUMENTS: NDA 050606; ANDA 062911; PIND 123456

TYPE OF SUBMISSION: New Drug Application - 505 (b)(2)

PURPOSE OF SUBMISSION: Original

SUMMARY AND RECOMMENDATIONS:

The applicant has submitted NDA 208910, Vancomycin Hydrochloride Powder for Oral Solution Kit (Firvanq®) for the treatment of *C. difficile* associated with diarrhea and for the treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains). The applicant is relying on the Agency findings of safety and efficacy of Vancomycin Hydrochloride Capsule USP (NDA 050606) and Vancomycin Hydrochloride for Injection USP (ANDA 062911) for this 505(b)(2) NDA.

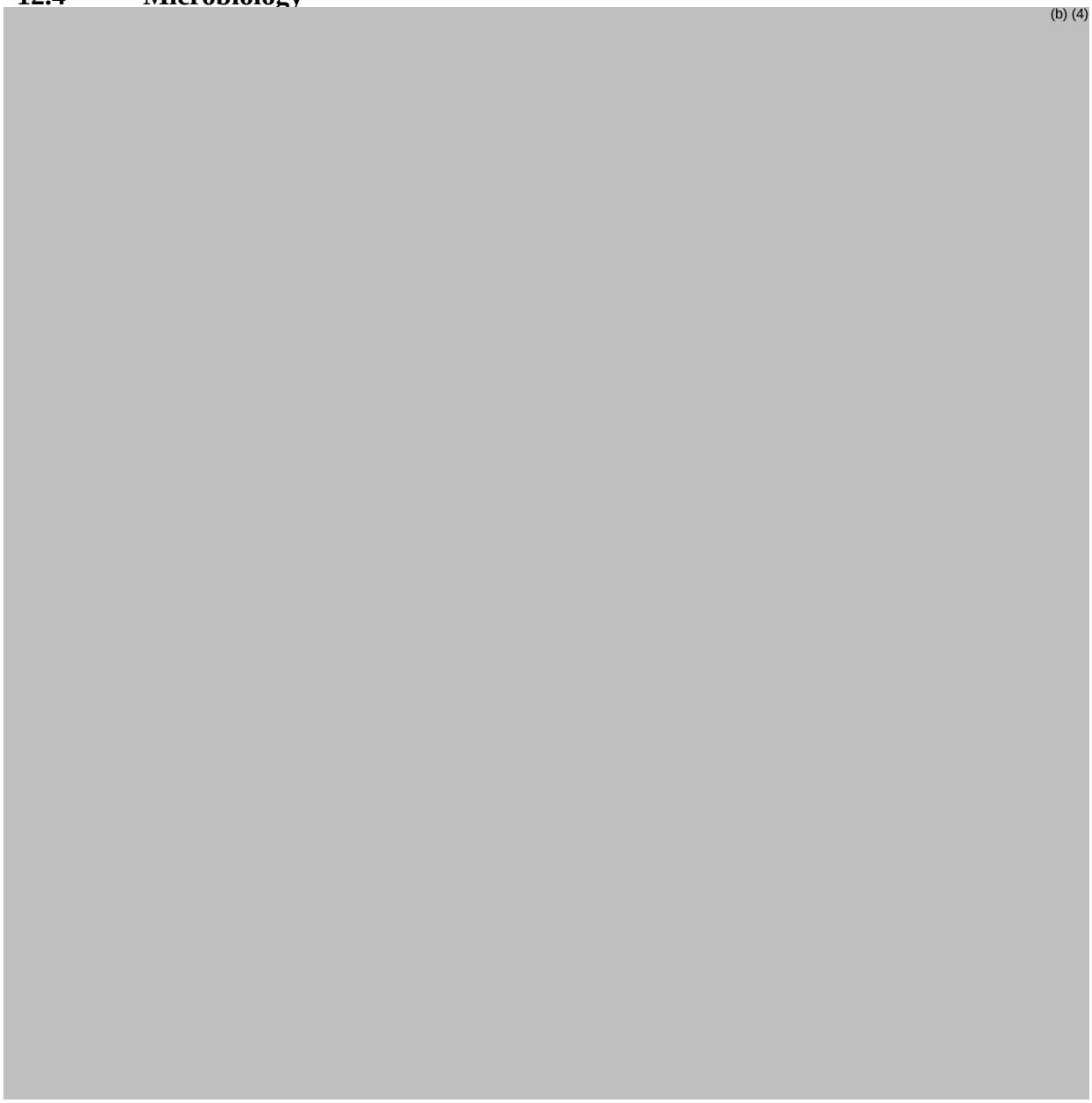
The application is recommended for approval pending acceptance of labeling changes to the MICROBIOLOGY subsection of the Package Insert shown below.

MICROBIOLOGY SUBSECTIONS OF THE PACKAGE INSERT

This Reviewer recommends changes to the Microbiology portion of the Package Insert as follows. Deletions have strikethrough; additions are in Red Font and double underlined.

12.4 Microbiology

(b) (4)



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Mechanism of action
The bactericidal action of vancomycin against *Staphylococcus aureus* and the vegetative cells of *Clostridium difficile* results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis.

Mechanism of resistance

Staphylococcus aureus
S. aureus isolates with vancomycin minimal inhibitory concentrations (MICs) as high as 1024 mcg/mL have been reported. The exact mechanism of this resistance is not clear but is believed to be due to cell wall thickening and potentially the transfer of genetic material.

Clostridium difficile
Isolates of *C. difficile* generally have vancomycin MICs of <1 mcg/mL, however vancomycin MICs ranging from 4 mcg/mL to 16 mcg/mL have been reported. The mechanism which mediates *C. difficile's* decreased susceptibility to vancomycin has not been fully elucidated.

Vancomycin has been shown to be active against susceptible isolates of the following bacteria in clinical infections as described in the *INDICATIONS AND USAGE* section.

Gram-positive bacteria
Staphylococcus aureus (including methicillin-resistant isolates) associated with enterocolitis.

Anaerobic gram-positive bacteria
Clostridium difficile isolates associated with *C. difficile* associated diarrhea.

EXECUTIVE SUMMARY:

Vancomycin is a glycopeptide antibiotic produced by *Amycolatopsis orientalis*. It inhibits cell wall synthesis in Gram positive bacteria and alters cell membrane permeability and RNA synthesis. Vancocin® capsule (vancomycin hydrochloride, USP; NDA 050606) is approved for the treatment of *C. difficile*-associated diarrhea and enterocolitis caused by *S. aureus* (including methicillin-resistant strains).

The applicant submitted a 505(b)(2) NDA for Vancomycin Hydrochloride Powder for Oral Solution Kit for the treatment of *Clostridium difficile*-associated diarrhea and enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains). The 505(b)(2) NDA relies on the Agency's safety and effectiveness findings for the reference listed drug, Vancocin® (vancomycin hydrochloride) oral capsules (NDA 050606) and reference standard Vancomycin Hydrochloride Injection, powder, lyophilized for solution, (ANDA 062911).

The applicant provided literature references to *in vitro* studies conducted with vancomycin and *C. difficile*. In addition, the applicant conducted a study to determine the minimum inhibitory concentration (MIC) of Vancomycin Oral solution reconstituted with grape flavored diluent (study MIC_14Nov 2016) against 100 strains of *C. difficile* and *S. aureus*. IV vancomycin hydrochloride and vancomycin hydrochloride capsules and (b) (4) laboratory standard were used as comparators. The study was conducted to support the request of waiver of *in vivo* bioavailability/bioequivalence studies. The MIC for the Vancomycin Oral solution was the same as or within one 2-fold dilution of the comparators.

The labeling for the microbiology subsection for the proposed product should reflect that of Vancocin® as oral vancomycin is not absorbed by gastrointestinal (GI) tract. There is no systemic exposure with oral vancomycin and systemic breakpoints do not apply.

SIGNATURES:

Kalavati Suvarna, Ph.D. {See appended signature}
Clinical Microbiology Reviewer Signature/Date

Avery Goodwin, Ph.D. . {See appended signature}
Acting Clinical Microbiology Team Leader Signature/Date

CC:
Original IND
MO/Patel, Sheral
CSO/Dean, Jane

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KALAVATI C SUVARNA
11/17/2017

AVERY C GOODWIN
11/21/2017