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APPLICATION NUMBER:

208910Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA#	208910
Product	FIRVANQ™ (Vancomycin Hydrochloride) Powder for Oral Solution Kit
Submission Date(s)	07/28/2017
Submission Type	505(b)(2)
Applicant	RxM™ Therapeutics LLC (a Wholly-Owned Subsidiary of CutisPharma, Inc.)
Primary Reviewer	Xiaohui (Tracey) Wei, Ph.D.
Secondary Reviewer	Zhixia (Grace) Yan, Ph.D.
OCP Division	DCP4
Medical Division	DAIP

Background

The Applicant submitted a 505(b)(2) New Drug Application (NDA) dated 07/28/2017 for FIRVANQ™ (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 kit is comprised of (b) (4) vancomycin hydrochloride USP and pre-measured Grape-Flavored Diluent and contains the equivalent to either 25 mg/mL or 50 mg/mL of vancomycin when reconstituted.

The Applicant relied on FDA's findings of safety and effectiveness of the listed vancomycin products for oral administration [i.e., Vancocin® Capsules (NDA 050606) and Vancomycin Hydrochloride for Injection USP (Hospira, Inc. ANDA 062911)]. The proposed indications for FIRVANQ™ are identical to the indications of reference listed drug (RLD), Vancocin® Capsules (NDA 050606).

The proposed dosing regimens as show in Table 1 are identical to the RLD of Vancocin® Capsules.

Table 1 Proposed dosing regimens for Vancomycin Hydrochloride Powder for Oral Solution Kit

Indication	Adults (≥18 years old)	Pediatrics (<18 years old)
<i>C. difficile</i> -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 <i>Staphylococcus aureus</i> (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.	

Owing to its low permeability, vancomycin hydrochloride is known to be poorly absorbed after oral administration and is intended to treat localized lower gastrointestinal (GI) tract infection.

No new clinical pharmacology information was submitted in this application, and the Applicant has submitted a request for waiver of providing evidence of in vivo bioequivalence of Vancomycin Hydrochloride Powder for Oral Solution Kit relative to RLDs as outlined in 21 CFR 320.22(d)(3). To support a waiver of in vivo bioequivalence study, the Applicant conducted in vitro solubility, permeability, dissolution and minimum inhibitory concentration (MIC) studies to bridge efficacy of the Vancomycin Hydrochloride Power for Oral Solution Kit and

Vancocin® Capsules (NDA 050606). Please refer to the Office of Pharmaceutical Quality (OPQ) Biopharmaceutics review for further evaluation of the request for waiver of bioequivalence requirements.

Because no new clinical pharmacology information was submitted to support this application, we focused our review on the labeling recommendations from the Clinical Pharmacology perspective.

Labeling Recommendations

The clinical pharmacology relevant information in the Applicant proposed labeling of FIRVANQ™ (b) (4). To improve the clarity and consistence of the labeling, the Office of Clinical Pharmacology recommends the following edits be included in the labeling:

- Under subsection 5.1 Oral Use Only from section 5 WARNINGS AND PRECAUTIONS, replace the statement of (b) (4)

We recommended these edits based on the considerations that although oral vancomycin hydrochloride is poorly absorbed in most patients, significant systemic absorption has been reported in some patients who have taken multiple oral doses of vancomycin hydrochloride for active *C. difficile* associated diarrhea as stated under section 5.2 Potential for Systemic Absorption in the label.

- Under subsection 5.2 Potential for Systemic Absorption from section 5 WARNINGS AND PRECAUTIONS, replace the following statement of (b) (4)

(b) (4) with “*Significant systemic absorption has been reported in some patients (e.g., patients with renal insufficiency and/or colitis) who have taken multiple oral doses of vancomycin hydrochloride for active C. difficile associated diarrhea. In these patients, serum vancomycin concentrations reached therapeutic levels for the treatment of systemic infections.*”

We recommended these edits and additions in order to clarify and elaborate the meaning of “(b) (4)”.

- Under section 12.3 Pharmacokinetics, replace the statement of (b) (4)

(b) (4) with “During multiple dosing of *vancomycin hydrochloride capsules* at 250 mg every 8 hours for 7 doses, fecal concentrations of vancomycin in volunteers exceeded 100 mcg/g in the majority of samples”. In addition, replace the statement of (b) (4) with “... concentrations of drug were > 3100 mcg/g in the feces...”.

We recommended these edits since the statement mentioned above is part of results from a study report included in the NDA 050606 for RLD of Vancocin® Capsules. The objective of this study was to determine the systemic and fecal availability of an oral

suspension versus an ^{(b) (4)} capsule formulation of vancomycin. This study report specified the 250 mg dose to be 250 mg capsules of vancomycin 8 hourly for seven doses. This study report also used unit of mcg/g instead of mg/kg to describe the fecal concentration of vancomycin.

Recommendation

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed the application. No new clinical pharmacology information was submitted. Recommended revisions on the proposed labeling are provided. This application is acceptable from a clinical pharmacology perspective.

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/s/

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01/09/2018

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01/09/2018