CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

2089100rig1s000

NON-CLINICAL REVIEW(S)

Memo to the Division File – Addendum to Review Submitted to DARRTS 1/10/2018

NDA 208910, Submitted 7/28/2017

Vancomycin Hydrochloride Powder for Oral Solution (RxM Therapeutics, LLC - Subsidiary of Cutis Pharma, Inc.)

From: Terry J. Miller, Ph.D., Pharmacology/Toxicology Reviewer, DAIP

Through: Jane Dean, RN, MSN, Regulatory Project Manager, DAIP

Date: Jan. 25, 2018

Recommendations:

The pharmacology/toxicology reviewer recommended adding a new sentence (underlined) to the drug labeling Subsection 8.1 **Pregnancy,** under the *Animal Data* subheading. This sentence is not to appear underlined in the final labeling.

> *Animal Data*
>
> Vancomycin did not cause fetal malformations when administered during organogenesis to pregnant rats (gestation days 6-15) and rabbits (gestation days 6-18) at the equivalent recommended maximum human dose (based on body surface area comparisons) of 200 mg/kg/day IV to rats or 120 mg/kg/day IV to rabbits. No effects on fetal weight or development were seen in rats at the highest dose tested or in rabbits given 80 mg/kg/day (approximately 1 and 0.8 times the recommended maximum human dose based on body surface area, respectively). Maternal toxicity was observed in rats (at doses 120 mg/kg and above) and rabbits (at 80 mg/kg and above).

The published source of this nonclinical study information can be found below:

Byrd, R.A., Gries, C.L., Buening, M. Developmental Toxicology Studies of Vancomycin Hydrochloride Administered Intravenously to Rats and Rabbits. Fundamental and Applied Toxicology 23, 590-597, 1994.

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/s/

TERRY J MILLER
01/25/2018

Memo to the Division File

NDA 208910, Submitted 7/28/2017

Vancomycin Hydrochloride Powder for Oral Solution (RxM Therapeutics, LLC - Subsidiary of Cutis Pharma, Inc.)

From: Terry J. Miller, Ph.D., Pharmacology/Toxicology Reviewer, DAIP

Through: Jane Dean, RN, MSN, Regulatory Project Manager, DAIP

Date: Jan. 09, 2018

Recommendations:

Pharmacology/Toxicology has no objection to the approval of NDA 208910 for Vancomycin Hydrochloride Powder for Oral Solution kit. Drug labeling Sections 8.1 **Pregnancy** and 8.2 **Lactation** should be revised as recommended by the DAIP review team to ensure compliance with PLR labeling requirements.

Background:

The Applicant, RxM Therapeutics, LLC., submitted a 505(b)(2) NDA to obtain marketing approval to license Vancomycin Hydrochloride Powder, for Oral Solution kit for treatment of *C.difficile*-associated diarrhea (CDAD) and enterocolitis caused by *S.aureus* infection. The kit is comprised of (b) (4) Vancomycin hydrochloride, USP and pre-measured Grape-flavored diluent to be reconstituted by the pharmacist. The Vancomycin USP powder and Grape-flavored diluent will be contained separately within HDPE bottles with a (b) (4) closure. The Applicant's vancomycin HCl product reconstituted as an oral solution will contain vancomycin hydrochloride equivalent to either 25 mg/mL or 50 mg/mL in a grape-flavored diluent (Table 1).

Table 1. Vancomycin HCl 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

(Applicant's Table 2.2-1 in Section 2.2 of the NDA)

The Applicant is relying on FDA's prior 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 Applicant submitted no new pharmacology/toxicology information to review. The planned clinical dosing regimen is identical to approved dosage in the labeling for the vancomycin oral capsule. An adult daily dosage of 500 mg to 2 g vancomycin HCl administered orally in 3 or 4 divided doses for 7-10 days; and a pediatric dose of 40 mg/kg in 3 or 4 divided doses for 7-10 days, not to exceed 2 g per daily total, is recommended in the labeling.

The Sponsor has identified (b) (4); DMF: (b) (4) and (b) (4) DMF: (b) (4)) as the two commercial sources of vancomycin hydrochloride drug substance; a letter of authorization from each DMF holder was included in the NDA. The Applicant is deferring to each DMF for the full description of the API including physical and chemical characteristics, manufacturing method, and specification and acceptance criteria required to ensure identity, strength, quality and purity. The Applicant also included a letter of authorization from (b) (4); DMF (b) (4)), the manufacturer of the Artificial Grape Flavor (b) (4). The quantitative composition of the Grape-flavored diluent is provided below (Table 2).

Table 2. Grape-Flavored Quantitative Composition

Name of Ingredient	Reference	Function	Quantity [% (w/v)]
Artificial Grape Flavor (b) (4)	DMF	(b) (4)	
D&C Yellow No. 10	21CFR 74.1710		
FD&C Red No. 40	21 CFR 74.1340		
Anhydrous Citric Acid	USP		
Sodium Benzoate	USP		
Sucralose	NF		
Purified Water	USP		

(Table 2.3.P.1-1 in Section 2.3.P. in the NDA)

All of the excipients in the Grape-flavored diluent have been incorporated into approved oral drug formulations found in the FDA's Drug Database of Inactive Ingredients for Approved Drug Products. The safety of all excipients in the Grape-flavored diluent are established for oral use at the proposed levels.

The Vancomycin HCl powder appears to be qualified to USP requirements by the manufacturer and the drug impurity profiles appear comparable to other commercially available oral vancomycin products. The overall acceptability of drug quality and the impurity specifications of both the drug substances and drug product are deferred to the

Chemistry review team. For additional information, refer to the FDA Chemistry review of the current NDA by the CMC reviewer, Dr. Yong Wang, in DARRTS.

The Applicant did not submit any new pharmacology / toxicology information for review in their 505(b)(2) NDA. No pharmacology/toxicology information was reviewed by the reviewer to support this 505(b)(2) NDA.

The Applicant referenced the FDA approved product labeling for the Reference Listed Drug (RLD) Vancocin® Capsules (NDA 050606; Ani Pharmaceuticals, Inc.) and modified the labeling to include PLR/PLLR compliant language in Section 8. The remaining pharmacology/toxicology relevant sections of the labeling, namely Section 13.1 **Carcinogenesis, Mutagenesis, Impairment of Fertility** appear consistent with the latest drug product labeling for the RLD Vancocin®. The Reviewer's proposed final labeling for Subsections 8.1 **Pregnancy** and 8.2 **Lactation** incorporating the recommendations from the clinical review team and from the Division of Pediatric and Maternal Health in CDER is provided below:

8 Use in Specific Populations

8.1 Pregnancy

Risk Summary

There are no available data on Firvanq use in pregnant women to inform a drug associated risk of major birth defects or miscarriage. Available published data on vancomycin use in pregnancy during the second and third trimesters have not shown an association with adverse pregnancy related outcomes *(see Data)*. Vancomycin did not show adverse developmental effects when administered intravenously to pregnant rats and rabbits during organogenesis at doses less than or equal to the recommended maximum human dose based on body surface area *(see Data)*.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

A published study evaluated hearing loss and nephrotoxicity in infants of pregnant intravenous drug users treated with vancomycin for suspected or documented methicillin-resistant staphylococcal aureus in the second or third trimester. The comparison groups were 10 non-intravenous drug-dependent patients who received no treatment, and 10 untreated intravenous drug-dependent patients served as substance abuse controls. No infant in the vancomycin exposed group had abnormal sensorineural hearing at 3 months of age or nephrotoxicity.

A published prospective study assessed outcomes in 55 pregnant women with a positive Group B streptococcus culture and a high-risk penicillin allergy with resistance to clindamycin or

unknown sensitivity who were administered vancomycin at the time of delivery. Vancomycin dosing ranged from the standard 1 g intravenously every 12 hours to 20 mg/kg intravenous every 8 hours (maximum individual dose 2 g). No major adverse reactions were recorded either in the mothers or their newborns. None of the newborns had sensorineural hearing loss. Neonatal renal function was not examined, but all of the newborns were discharged in good condition.

Animal Data

Vancomycin did not cause fetal malformations when administered during organogenesis to pregnant rats (gestation days 6-15) and rabbits (gestation days 6-18) at the equivalent recommended maximum human dose (based on body surface area comparisons) of 200 mg/kg/day IV to rats or 120 mg/kg/day IV to rabbits. No effects on fetal weight or development were seen in rats at the highest dose tested or in rabbits given 80 mg/kg/day (approximately 1 and 0.8 times the recommended maximum human dose based on body surface area, respectively). Maternal toxicity was observed in rats (at doses 120 mg/kg and above) and rabbits (at 80 mg/kg and above).

8.2 Lactation

Risk Summary

There are insufficient data to inform the levels of vancomycin in human milk. However, systemic absorption of vancomycin following oral administration is expected to be minimal *[see Clinical Pharmacology (12.3)]*. There are no data on the effects of Firvanq on the breastfed infant or milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Firvanq and any potential adverse effects on the breastfed infant from Firvanq or from the underlying maternal condition.

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/s/

TERRY J MILLER
01/10/2018