

## MEMORANDUM

**Date:** April 9, 2012

**To:** Vancomycin File

**From:** CDER Exclusivity Board

**Subject:** Analysis and Recommendation Regarding Eligibility for Three-Year Exclusivity – Vancocin® (vancomycin hydrochloride capsules) Supplement 28 (sNDA 50-606/S-028)

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The Exclusivity Board within the Center for Drug Evaluation and Research (CDER) has analyzed the eligibility of Vancocin® (vancomycin hydrochloride capsules) for three years of exclusivity against generic competition pursuant to section 505(j)(5)(F)(iv) of the Federal Food, Drug and Cosmetic Act (FD&C Act). Based on its analysis, the Exclusivity Board recommends that the labeling changes for Vancocin capsules approved by FDA on December 14, 2011, in Supplemental New Drug Application (sNDA) 50-606/S-028, do not entitle Vancocin to three years of exclusivity, because of limitations on such exclusivity for certain antibiotic products set forth in section 505(v) of the FD&C Act.

In making its recommendation, the Exclusivity Board reviewed the applicable law; the labeling changes approved in the sNDA; a December 22, 2011 supplement filed by ViroPharma to its citizen petition (FDA-2006-P-0007) in favor of Vancocin's eligibility for 3-year exclusivity (the "ViroPharma Dec. 22, 2011 CP Supplement"); memoranda by the Division of Anti-Infective Products (DAIP or the "Division") on the clinical data submitted in the sNDA; and a written reply by DAIP to a consult by the Office of Regulatory Policy (ORP). DAIP's memoranda and its written reply are incorporated herein in their entirety.<sup>1</sup>

A discussion of the Exclusivity Board's reasoning follows.

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<sup>1</sup> Memoranda to OCC and ORP submitted by Benjamin Lorenz, MD (OND/OAP/DAIP) on December 12, 2011, and December 15, 2011; Written Reply to ORP Consult submitted by Ben Lorenz dated April 9, 2012. (see attachments).

## I. BACKGROUND

### a. Approval of sNDA 50-606/S-028 for Vancocin

Vancocin (vancomycin hydrochloride (HCl)) capsules were first approved in 1986 for the treatment of antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile* (*C. difficile*) and for the treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains). On December 14, 2011, FDA approved Supplemental New Drug Application (sNDA) 50-606/S-028 for Vancocin capsules. This “Prior Approval” Efficacy Supplement<sup>2</sup> sought updates to the prescribing information in Vancocin labeling, supported by two Phase 3 clinical safety and efficacy studies conducted by Genzyme, Inc. (Genzyme), the exclusive rights to which were purchased by ViroPharma.

The two Phase 3 trials (GD3-170-301 and GD3-170-302, also referred to as “the Genzyme studies”) were conducted to evaluate the safety and efficacy of the investigational comparator tolevamer for the treatment of *Clostridium difficile*-associated diarrhea (CDAD) using vancomycin capsules and metronidazole (Flagyl) as the active comparators. The two trials failed to show that tolevamer was effective in the treatment of CDAD; however, there was evidence of the activity of Vancocin at a dose of 125 mg q.i.d. for 10 days. It was thus decided that the efficacy results for the comparison between Vancocin and tolevamer, where tolevamer represented a putative placebo, could be submitted in support of requested labeling changes for Vancocin. It should be noted that no new CMC, pharmacology/toxicology, clinical pharmacology, or clinical microbiology was contained in the sNDA.

Changes to the “Indications and Usage,” “Dosage and Administration,” and “Adverse Reactions” sections, and new sections on clinical studies, nephrotoxicity and geriatric use were approved in the sNDA. In addition, the labeling changes in the supplement brought the Vancocin labeling into compliance with the Physician Labeling Rule (PLR).<sup>3</sup>

The Agency did not make an exclusivity determination when the sNDA was approved. ViroPharma subsequently filed a supplement on December 22, 2011 to a pending citizen petition (FDA-2006-P-0007) asserting, among other things, that as a result of the modified labeling, Vancocin is entitled to three years of exclusivity against generic competition pursuant to section 505(j)(5)(F)(iv) of the FD&C Act (ViroPharma Dec. 22, 2011 CP Supplement at 1).

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<sup>2</sup> Prior approval efficacy supplements are described in 21 CFR 314.70(d).

<sup>3</sup> *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, Food & Drug Administration, 71 Fed. Reg. 3922 (Jan. 24, 2006), promulgated in 21 CFR 201.56, 201.57.

## b. Labeling Changes

Appendix A to this memorandum shows the labeling changes that ViroPharma addressed in its December 22 CP supplement and that are relevant to the determination of exclusivity. For purposes of this analysis, we have focused on the changes in the “Indications and Usage” and “Dosage and Administration” sections of the labeling, which are reproduced below in their entirety.

### INDICATIONS & USAGE

VANCOGIN HCl Pulvules ~~may be administered orally~~ CAPSULES are indicated for the treatment of ~~enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) and antibiotic associated pseudomembranous colitis caused by *C. difficile*~~ ~~–associated diarrhea.~~

VANCOGIN CAPSULES are also used for the treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains).

### DOSAGE & ADMINISTRATION

#### Adults

~~Oral Vancocin HCl~~ VANCOGIN CAPSULES is used in treating ~~antibiotic-associated pseudomembranous colitis caused by *C. difficile*~~ ~~–associated diarrhea~~ and staphylococcal enterocolitis. ~~The usual adult total daily dosage is 500 mg to 2 g administered orally in 3 or 4 divided doses for 7 to 10 days.~~

- *C. difficile*-associated diarrhea: The recommended dose is 125 mg administered orally 4 times daily for 10 days.<sup>4</sup>
- Staphylococcal enterocolitis: Total daily dosage is 500 mg to 2 g administered orally in 3 or 4 divided doses for 7 to 10 days.

#### Pediatric Patients

The usual daily dosage is 40 mg/kg in 3 or 4 divided doses for 7 to 10 days. The total daily dosage should not exceed 2 g.

As shown, “treatment of . . . antibiotic-associated pseudomembranous colitis caused by *C. difficile*” is now described as “treatment of . . . *C. difficile*-associated diarrhea [(CDAD)].” In lieu of stating that Vancocin “may be administered orally for treatment of” enterocolitis caused by *S. aureus*, the new labeling now states that Vancocin capsules “are also used for the treatment of” enterocolitis caused by *S. aureus*.

The broad dosing regimen for Vancocin (which previously combined dosing for *C. difficile*-associated diarrhea in adults and staphylococcus aureus) was separated out by indication such that only one dosage was selected from the previous broad regimen of

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<sup>4</sup> 125 mg “4 times daily” is also referred to as “125 mg q.i.d.” The acronym “q.i.d.” which stands for “*quarter in die*” is the medically recognized Latin term for 4 times daily.

“500 mg to 2 g administered orally in 3 or 4 divided doses for 7 to 10 days” *C. difficile*-associated diarrhea in adults (“125 mg administered orally 4 times daily for 10 days”), while remaining the same for staphylococcus aureus. The descriptor “usual” used to qualify the total daily dosage in adults was deleted.

### **c. Relevant Statutory and Regulatory Framework**

The availability of a three-year exclusivity period for supplements to previously approved drug products is described in section 505(j)(5)(F)(iv) of the FD&C Act.<sup>5</sup> It provides that “[i]f a supplement to an application approved under subsection (b) . . . contains reports of new clinical investigations (other than bioavailability studies) *essential to the approval* of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b)” (emphasis added).<sup>6</sup>

For purposes of exclusivity determinations, the Agency interprets the phrase “new clinical investigations” to mean an investigations conducted on humans “the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.”<sup>7</sup> In addition, the Agency interprets the phrase “essential to approval” to mean that “with regard to an investigation . . . there are no other data available that could support approval of the application.”<sup>8</sup> In other words, the change could not be approved without the investigation.

Certain changes to some antibiotic products are, however, not eligible for the three-year exclusivity protection provided by section 505(j)(5)(F)(iv) of the FD&C Act. Specifically, section 505(v) of the FD&C Act provides that “Old Antibiotics” (those antibiotic drugs for which the first application was received before the enactment of the *Food and Drug Modernization Act of 1997* (FDAMA) on November 21, 1997) are not eligible for the three-year exclusivity period for “any condition of use” for which the Old Antibiotic was approved before October 8, 2008 (the date of the enactment of the *QI*

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<sup>5</sup> A parallel provision regarding delay of 505(b)(2) applications due to three-year exclusivity is found at 505(c)(3)(E)(iv) of the FD&C Act.

<sup>6</sup> Section 505(j)(5)(F)(iv) of the FD&C Act. See also 21 CFR 314.108(b)(5).

<sup>7</sup> 21 CFR 314.108(a).

<sup>8</sup> *Id.*

*Program Supplemental Funding Act of 2008* (the QI Act), the statute that amended the FD&C Act to create section 505(v).<sup>9</sup>

The statute does not define the phrase “condition of use.” Based on FDA’s scientific and medical expertise, however, as well as our review of the statute and available legislative history, FDA defines “condition of use,” as used in section 505(v)(3)(B) of the FD&C Act, to mean a significant new use for an Old Antibiotic, such as a new indication, not merely minor differences in labeling related to previously approved uses for Old Antibiotics.<sup>10</sup>

## **II. ViroPharma’s Claims**

### **a. ViroPharma’s Argument That Section 505(v) of the FD&C Act Provides Exclusivity as an Incentive for Old Antibiotics such as Vancocin**

ViroPharma asserts that Vancocin is eligible for the three-year exclusivity period because among other things, Congress amended the FD&C Act to add section 505(v) “to permit . . . [three-]year exclusivity for ‘old’ antibiotics like Vancocin” (see ViroPharma Dec. 22, 2011 CP Supplement at 4), Congress intended that the incentives available under section 505(v) “be maximally available to antibiotic manufacturers” (id. at 9), and that “[r]ecognizing that ViroPharma’s investment in new investigations to update Vancocin’s labeling has earned . . . [three-]year exclusivity will help cement this incentive as a means to attract further investment in research on older antibiotics” (id.).

ViroPharma contends that Vancocin’s labeling has undergone “fundamental and extensive changes” that constitute “numerous new conditions of use” for Vancocin. Specifically, the company contends that the Vancocin labeling changes included, among other things, (1) a new indication of use, because the CDAD indication changed from “treatment of antibiotic-associated pseudomembranous colitis caused by *C. difficile*” to “treatment of *C. Difficile*-associated diarrhea;” (2) a new dosing regimen for CDAD patients, because the dosage and administration of the 125 mg capsules changed from “500 mg to 2 g administered orally [in 3 or 4 divided doses] for 7-10 days” to “125 mg orally 4 times a day for 10 days;” and (3) new information based on the clinical study data submitted in the sNDA, including information on adverse reactions, detailed information on nephrotoxicity, and detailed information regarding the use of Vancocin in geriatric patients. (Id. at 6-7.)

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<sup>9</sup> Section 505(v)(3)(B) of the FD&C Act. For a more detailed discussion of the genesis of exclusivity protections accorded to antibiotic drug products, please refer to the Agency’s April 9, 2012 response to citizen petition FDA-2006-P-0007.

<sup>10</sup> For a more detailed discussion of FDA’s interpretation of the “conditions of use” for which Old Antibiotics are not eligible for three-year exclusivity, please refer to the Agency’s April 9, 2012 response to citizen petition FDA-2006-P-0007.

**b. ViroPharma’s Argument that Vancocin has a New Approved Indication**

ViroPharma claims that the prior *C. difficile* indication was changed based on the new studies, such that Vancocin is now “indicated for the treatment of *C. difficile*-associated diarrhea [(CDAD)]” (see ViroPharma Dec. 22, 2011 CP Supplement at 7). ViroPharma states that the new Clinical Studies section explains what is meant by “*C. difficile*-associated diarrhea” in the new studies that led to this changed indication, as well as the efficacy endpoint by which resolution of CDAD was measured. (See ViroPharma Dec. 22, 2011 CP Supplement at 7.) CDAD as defined in the Clinical Studies section is “as three or more loose or watery bowel movements within the 24 hours preceding enrollment, plus the presence of *C. difficile* toxins or pseudomembranes on endoscopy.”

ViroPharma asserts that the Genzyme studies were essential to approval of these changes, and that clinical trials conducted to support the approval of NDA 201699 for Dificid (fidaxomicin), and publicly available in peer-reviewed article in the *New England Journal of Medicine*<sup>11</sup> (collectively the “Dificid studies”) could not have supported these changes because: (1) they were different in design, entry criteria, and efficacy endpoint from the new Genzyme studies (see *id.* at 11); and (2) they were statistically powered to show that Dificid is not inferior to Vancocin (by virtue of the protocol definitions of CDAD and cure in the Dificid studies), rather than to demonstrate Vancocin efficacy, which was assumed (*id.*).

Specifically, with respect to trial design, ViroPharma contends that the Dificid studies (Phase 3 non-inferiority studies comparing fidaxomicin with vancomycin in patients with *C. difficile* infection) did not replicate the “unique result of the new Vancocin studies [Genzyme studies]: demonstration of Vancocin efficacy against a (‘putative’) placebo,” *i.e.*, tolevamer, and were in fact “active-controlled” against fidaxomicin. (See *id.*) Moreover, ViroPharma contends that Vancocin’s CDAD indication (as defined in the new Clinical Studies section) is different from the Dificid definition of CDAD which requires four or more unformed bowel movements in the 24 hours before randomization, as well as the presence of *C. difficile* toxins which could not be replaced by pseudomembranes on endoscopy. (*id.*) Finally, ViroPharma contends that the efficacy of Vancocin (125 mg q.i.d.) against CDAD was also assessed differently in the Dificid studies. (*id.*) Specifically, according to ViroPharma, the Genzyme studies defined treatment success as “two or fewer loose or unformed bowel movements and the absence of severe abdominal discomfort due to CDAD, a unique co-primary endpoint requested by FDA,” whereas the Dificid studies, defined clinical success as an “improvement in diarrhea or other symptoms such that, in the Investigator’s judgment, further CDAD treatment was not needed” (See *id.* at 11 -12). Moreover, according to ViroPharma, the studies also varied greatly in the clinical history of the patients and the severity of the disease which could have had a large impact on the clinical success rate (See *id.* at 12, note 56).

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<sup>11</sup> Louie, T.J., Miller, M.A., Mullane, K.M., *et al.* Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med.* 2011; 364(5):422-431 (Louie, T.J., *et al.*) (also referred to as “the publicly available documentation of the Dificid Studies”).

ViroPharma also claims that “[i]n light of the two new CDAD studies, the Indications and Usage section was also modified to reflect the relative absence of data for *S. aureus* enterocolitis, which is no longer referred to as an indication in the new labeling” (See *id.* at 7). Indeed, ViroPharma argues that Vancocin’s labeling does not state that Vancocin is “indicated for” *S. aureus*, but merely advises that Vancocin is “also used for the treatment of *S. aureus*. (See *id.* at 21). Thus, ViroPharma concludes that “the labeling language regarding Vancocin usage in the treatment of *S. aureus* does not meet the indication regulation’s requirement [21 CFR § 201.57(c)(2)] that labeling ‘must state that the drug is indicated for the treatment’ of *S. aureus*” (*id.*).

**c. ViroPharma’s Argument that Vancocin has a New Approved Dosing Regimen**

ViroPharma claims that the “[t]he new Vancocin labeling . . . for the first time specifies a recommended dosing regimen” (see ViroPharma Dec. 22, 2011 CP Supplement at 1) “of 125 mg q.i.d., the dose demonstrated to be safe and effective in the new studies” (see *id.* at 6).

Specifically, ViroPharma claims that:

The new Vancocin studies [Genzyme studies] led to the significant modification of Vancocin's previously labeled “usual” 500 mg to 2 g CDAD daily dosing range. For the first time Vancocin is now labeled with a “recommended” CDAD dose: 125 mg four times daily for ten days, based on the dose used in the two new studies submitted in the Vancocin sNDA, which also removed the word “usual” from the *S. aureus* dosing range due to data insufficiency concerns.

(See *id.* at 7).

**d. ViroPharma’s Argument that the Genzyme Studies were Essential to the Inclusion of Certain Information in the New Labeling**

ViroPharma argues that the Genzyme studies were essential to inclusion of nephrotoxicity information in the labeling, including information regarding nephrotoxicity in general, nephrotoxicity in the geriatric population, and monitoring of renal function. Specifically, ViroPharma states that based on the studies submitted in the new Vancocin sNDA, the labeling now specifically warns that “[n]ephrotoxicity (e.g., reports of renal failure, renal impairment, blood creatinine increased) has occurred following oral VANCOGIN therapy in randomized controlled clinical studies, and can occur either during or after completion of therapy.” (See ViroPharma Dec. 22, 2011 CP Supplement at 6.)

Regarding the use of Vancocin in geriatric patients, ViroPharma states that the subsection on geriatric use is wholly rewritten based on the new data and while the old labeling merely stated that “[t]he risk of nephrotoxicity is increased in patients >65 years of age” (See p 6), the new labeling “now lists the percentage of patients in the new studies who

were >65, between >65 and 75, and >75, the increased risk of nephrotoxicity in geriatric patients seen in the new studies, and the associated instruction that renal function should be monitored in all elderly both during and following treatment.” (See *id.* at 7.)

Finally, regarding the monitoring for renal dysfunction, ViroPharma notes that whereas the old labeling merely stated that “[w]hen patients with underlying renal dysfunction or those receiving concomitant therapy with an amino glycoside are being treated, serial monitoring of renal function should be performed,” the new label states the need to monitor renal function in all patients (see *id.* at 5), and provides more specific monitoring regimens. Specifically, the new labeling states that “[i]n patients >65 years of age, including those with normal renal function prior to treatment, renal function should be monitored during and following treatment with VANCOCIN to detect potential vancomycin induced nephrotoxicity,” (See *id.* at 6.) ViroPharma also asserts that the new labeling notes that “the new studies showed geriatric patients may take longer to respond to therapy, and as a result advises that ‘[c]linicians should be aware of the importance of appropriate duration of VANCOCIN treatment in patients >65 years.’” (See *id.* at 7.) ViroPharma further notes that the new labeling “reports the median day of nephrotoxicity onset” (see *id.* at 6), and advises of “a longer median time to resolution in geriatric patients” (see *id.* at 5), and, thus, includes a warning to clinicians “to be aware of the importance of not prematurely discontinuing Vancocin treatment in the elderly” (*id.*). ViroPharma asserts that such information did not exist prior to the recent Vancocin sNDA, and is thus wholly based on the new clinical data submitted in the sNDA (see *id.* at 6), thus making the Genzyme studies essential to approval of this information in the labeling.

ViroPharma also asserts that the information on clinical success rates in the hypervirulent B1 strain, as well as recurrence of CDAD during the four weeks following diarrhea resolution at end-of-treatment with Vancocin is not supportable by data other than that obtained in the Genzyme Studies. (*id.*)

### **III. Discussion**

#### **a. Vancocin is Not Eligible for Three-Year Exclusivity Due to the Limitation on Such Exclusivity Set Forth in Section 505(v) of the FD&C Act.**

The Exclusivity Board concludes that revision of the Vancocin labeling to incorporate clinical data regarding already approved conditions of use does not constitute approval for a “new condition of use” within the meaning of 505(v). Therefore, these labeling changes do not merit three-year exclusivity under the limitation on such exclusivity for an Old Antibiotic product subject to section 505(v)(3) of the FD&C Act.

First, Vancocin’s modified labeling does not support or reflect a new or changed indication for the product. “Antibiotic-associated pseudomembranous colitis caused by *C. difficile*” and “*C. difficile*-associated diarrhea” are not mutually exclusive indications. “Pseudomembranous colitis” implies that the diagnosis was made pathologically (via endoscopy), rather than a clinical diagnosis using the toxin assay in stool. However, in



general clinical practice, diagnoses are typically made based upon a positive *C. difficile* toxin assay associated with diarrhea (as they were in the Genzyme studies), and may not necessarily be associated with the prior use of antibiotics. Thus, the labeling changes only clarified the previously approved indication; they did not constitute a new indication.

Second, ViroPharma's claim that the new labeling included a new dosing regimen does not support a grant of exclusivity. The dosing regimen that ViroPharma claims as new – "125 mg orally 4 times a day for 10 days" – is encompassed within the prior regimen of "500 mg to 2 g administered orally in 3 or 4 divided doses for 7-10 days." This change to the label is not an innovation; rather, "125 mg administered 4 times daily" dose of vancomycin has been adopted as the "standard dose" since the 1980s.<sup>12</sup> Antibiotic guides, such as the *Sanford Guide to Antimicrobial Therapy*, recommend the "125 mg po qid × 10-14 days" regimen (as listed for "*C. difficile* toxin positive antibiotic-associated colitis").<sup>13</sup>

Finally, labeling changes related to clinical study data for CDAD, nephrotoxicity and geriatric use merely relate to and provide additional details regarding the previously approved indication for treatment of CDAD in already identified patient populations. These changes do not constitute a new use of the product.

**b. The Labeling Changes in the Indications and Usage Section Do Not Reflect a New Approved Indication for Vancocin.**

The Exclusivity Board disagrees with ViroPharma's assertions that the labeling changes in the Indications and Usage section reflect a new approved indication for Vancocin for the reasons stated above. Moreover, the Genzyme studies do not appear to be essential to the approval of these labeling changes; the publicly available documentation of the Dificid studies also provide adequate support for this labeling change.

Although minor differences in comparators, statistical design definition of CDAD and treatment success exist between the Dificid studies and the Genzyme studies, both trials ultimately support the use of vancomycin at the same dosage and administration for the same indication. Moreover, both studies recruited patients with sufficient overlapping clinical characteristics to be comparable (see Table 1 below, for comparison of baseline characteristics between the two trials). Specifically, the Genzyme studies defined CDAD as three or more loose or watery bowel movements within the 24 hours preceding enrollment, and the presence of *C. difficile* toxins *or* pseudomembranes on endoscopy; the Dificid studies required four or more unformed bowel movements in the 24 hours before randomization, and mandated the presence of *C. difficile* toxins (i.e., a finding of pseudomembranes on endoscopy could not replace a positive *C. difficile* toxin assay

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<sup>12</sup> Bartlett, et al.

<sup>13</sup> Gilbert, D.N., Moellering, R.C., Eliopoulos, G.M., Chambers, H.F., Saag, M.S., , *The Sanford Guide to Antimicrobial Therapy* 41st ed. Sperryville, VA. Antimicrobial Therapy; 2011:16 (hereinafter "Gilbert et al, The Sanford Guide to Antimicrobial Therapy").

associated with diarrhea). The Genzyme studies, however, did not present any data in their integrated analysis to account for how many patients were included on the basis of endoscopic findings, in lieu of a presence of toxin in the stool, and in any case, as stated above, diagnoses in current clinical practice are usually confirmed by presence of toxin in the stool regardless of whether endoscopy is performed.

**Table 1: Baseline Characteristics: Comparison of CDAD definition between Trials**

	<b>Genzyme (Full Analysis Set)*</b>	<b>Dificid (mITT population)†</b>
Mild	75 (29.0%)	176 (31.3%)
Moderate	118 (45.6%)	176 (31.3%)
Severe	65 (25.1%)	211 (37.4%)
Missing	1 (0.4%)	0

Genzyme: Mild = 3-5 bowel movements (BM)/day; Moderate = 6-9 BM/day; Severe =  $\geq 10$  BM/day.

† Dificid: Mild = 4-5 BM/day; Moderate = 6-9 BM/day; Severe  $\geq 10$  BM/day

Although ViroPharma asserts that the Genzyme studies demonstrate the drug’s comparative efficacy against a “putative placebo,” the new labeling is only descriptive in nature with no mention of the “putative placebo.” It should be noted that the Genzyme studies were originally designed to test the primary hypothesis of efficacy for tolevamer in comparison to vancomycin and metronidazole, with the comparison of vancomycin with metronidazole serving only as a secondary analysis. Thus, any comparison of vancomycin with tolevamer (the “putative placebo”) or metronidazole would have been considered a secondary analysis and therefore (b) (4)

(b) (4) In light of these limitations, and in keeping with conclusions drawn from the review of the submission for the first cycle, the Division determined that only descriptive (b) (4) efficacy analyses from the Genzyme studies were appropriate to be included in the labeling. The Division notified ViroPharma of this conclusion at a final labeling teleconference with the company on December 8, 2011. Consequently, the revised proposal ViroPharma submitted for the Clinical Studies section contained a summary of the trials’ outcomes (b) (4).

The Exclusivity Board also disagrees with ViroPharma’s contention that the treatment of *S. aureus* “is no longer referred to as an indication in the new labeling” (See ViroPharma Dec. 22, 2011 CP Supplement at 21). The old labeling stated that Vancocin “may be administered orally for treatment of enterocolitis caused by . . . [*S. aureus*],” while the new labeling states that the drug is “also used for the treatment of enterocolitis caused by . . . [*S. aureus*].” No new clinical data or other information was presented in the sNDA in relation to *S. aureus*, and no significant addition or omission in the labeling was made with respect to *S. aureus*. This minor change in syntax between the old and the new labels does not bear evidence to ViroPharma’s contention that the treatment of *S. aureus* is no longer referred to as an indication in the new labeling. In substance, the information in the new labeling remains unchanged.

**c. The Labeling Changes in the Dosage and Administration Section Do Not Reflect a New Approved Dosing Regimen for Vancocin.**

As stated above, the Exclusivity Board believes that the 125 mg q.i.d. dosage for the treatment of CDAD in adults is neither a new recommended dose (i.e. outside of the range of the currently approved dose) nor a regimen for a new indication. Moreover, the medical literature has long shown the 125 mg q.i.d. dose to be optimal. For instance, while higher doses have been shown to achieve greater fecal concentrations, there is no evidence that higher dosing regimens offer any clinical benefit in treating CDAD.<sup>14,15,16</sup> As discussed in the 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA), “[v]ancomycin is the drug of choice for an initial episode of severe CDI<sup>17</sup> [*Clostridium difficile* infection]. The dosage is 125 mg orally 4 times per day for 10–14 days.<sup>18</sup>

Thus, there exists ample evidence that the 125 mg q.i.d. dose to treat CDAD, which has always been encompassed in the vancomycin labeling, has been the standard, preferred dosage recommended for and by physicians for the treatment of CDAD. The Genzyme studies merely support the previous findings that this dosage is an effective regimen. Although the Genzyme studies used the lower dose of 125 mg four times daily (for a mean duration of 9.4 days), they did not compare different dosing regimens of vancomycin. In contrast, other clinical investigations have compared different dosage regimens of vancomycin.<sup>19,20</sup> Moreover, many clinical investigations have shown that the 2.0 g daily regimen has not been shown to provide an advantage (whether for primary

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<sup>14</sup> Baird, D.R., Comparison of two oral formulations of vancomycin for treatment of diarrhoea associated with *Clostridium difficile*. *J Antimicrob Chemother.* 1989; 23(1): 167-169 (Baird).

<sup>15</sup> Keighley, M.R., Burdon, D.W., Arabi, Y., Alexander-Williams, J., Thompson, H., Youngs, D., Johnson, M., Bentley, S., George, R.H., Mogg, G.A., Randomised controlled trial of vancomycin for pseudomembranous colitis and postoperative diarrhoea. *Br Med J.* 1978; 2: 1667-1669 (Keighley, et al.).

<sup>16</sup> Thielman, N.M., Wilson, K.H., 2010. Antibiotic-Associated Colitis, p. 1375–1387. In GL Mandell, JE Bennett, and R Dolin (eds.), *Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases*. Elsevier, Philadelphia, PA (Thielman et al.).

<sup>17</sup> Note that the terms CDI and CDAD are interchangeable (see Footnote 28).

<sup>18</sup> Cohen, S.H., Gerding, D.N., Johnson, S., et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol.* 2010; 31(5):431-455 (Cohen et al.).

<sup>19</sup> Fekety, R., Silva, J., Kauffman, C., Buggy, B., Deery, H.G., Treatment of antibiotic-associated *Clostridium difficile* colitis with oral vancomycin: comparison of two dosage regimens. *Am J Med.* 1989; 86(1):15-19 (Fekety et al.).

<sup>20</sup> Zar, F.A., Bakkanagari, S.R., Moorthi, K.M., Davis, M.B., A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis.* 2007; 45(3):302-307 (Zar et al.).

or recurrent, or for mild or severe disease).<sup>21</sup> Thus, although the Genzyme studies support the previous findings that the lower dose is an effective regimen for CDAD, the inclusion of only the 125 mg q.i.d. dose in the Dosage and Administration section of the prescribing information is supported by the totality of the available evidence; the clinical trials submitted in the sNDA were not essential to the approval of this change.

Of note, there is no approved dosage specifically for pediatric patients in the treatment of CDAD. Had this labeling change to the dosage and administration section been a “new dosing regimen,” or had the change in the description of *C. difficile* been a new indication this sNDA would have triggered the Pediatric Research Equity Act (PREA) (Section 505B of the FDCA), and pediatric trials in patients with CDAD would have been required. Neither ViroPharma nor the agency believed that this was a new dosing regimen, so ViroPharma did not address PREA with the submission of pediatric studies or a request for waiver or deferral and submission of a pediatric plan, and the agency did not hold up the filing or the approval of the sNDA because of this omission.

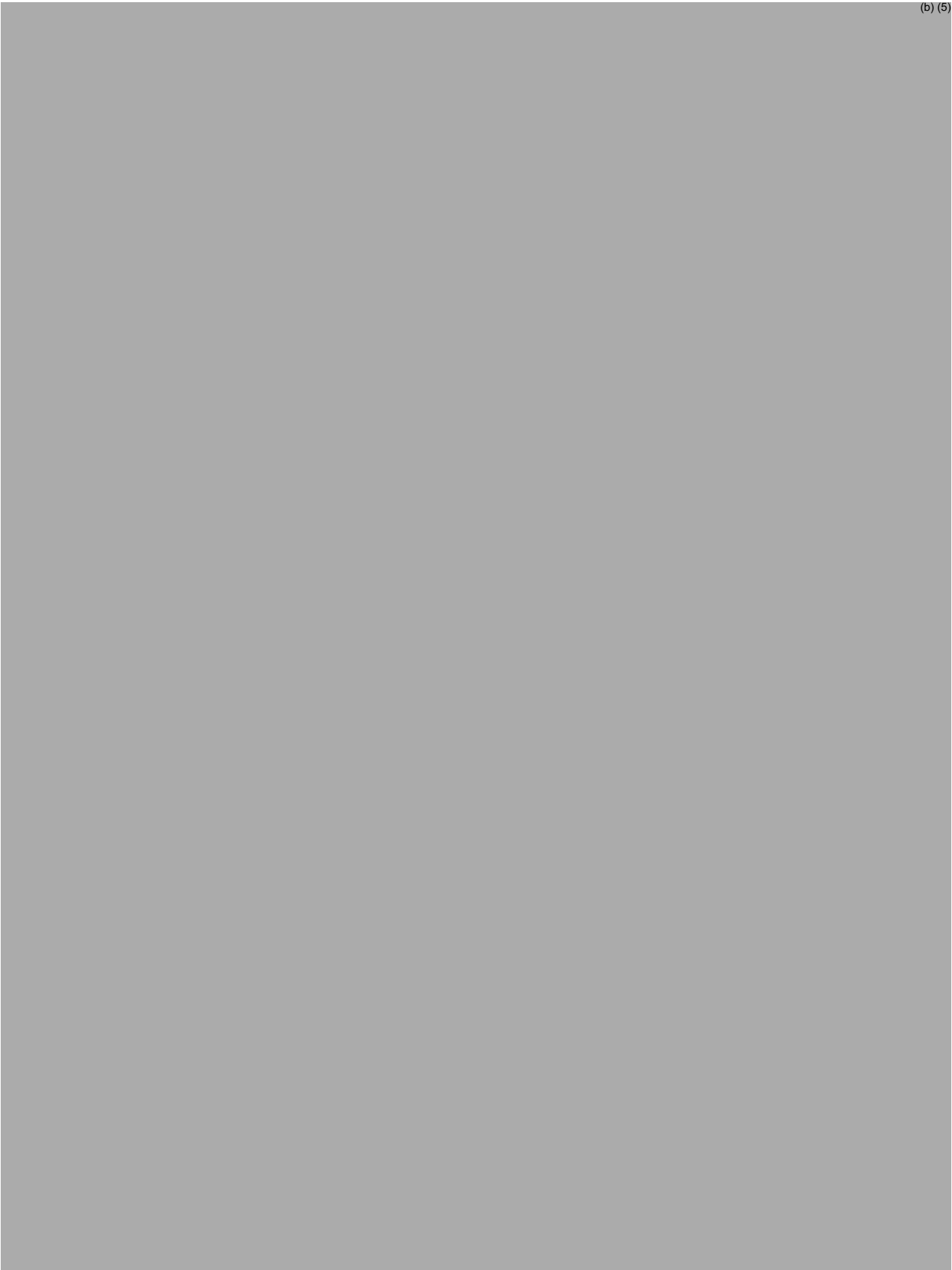
Finally, language modifications to the dosing directions for *Staphylococcus aureus* enterocolitis (SAE) were made to conform to the format set forth in the PLR. The Genzyme studies did not include any new data for patients with staphylococcal enterocolitis. The indication in the current labeling remains with only minor change in syntax: “Staphylococcal enterocolitis: Total daily dosage is 500 mg to 2 g administered orally in 3 or 4 divided doses for 7 to 10 days.” Removal of the word “usual” is not a change that reflects new findings from clinical data and was merely in response to a recommendation from the Division of Drug Marketing, Advertising and Communications (DDMAC).<sup>22</sup>

(b) (5)

With regard to the statements in the new labeling on nephrotoxicity in general, nephrotoxicity in the geriatric population, and monitoring of renal function, these do not represent new conditions of use within the meaning of 505(v).

<sup>21</sup> Baird; Keighley et al.; Thielman et al., Wilson et al.; and Fekety et al.

<sup>22</sup> DDMAC is now referred to as the Office of Prescription Drug Promotion (OPDP).



(b) (5). Because this information is descriptive only, the Exclusivity Board believes that this labeling change does not represent a new condition of use for an Old Antibiotic sufficient to support exclusivity under 505(v).



#### **IV. CONCLUSION**

Under FDA’s interpretation of the applicable statutory and regulatory authorities governing the limitations on three-year exclusivity for Old Antibiotics such as Vancocin, the Exclusivity Board has concluded that the labeling changes approved in sNDA 50-606/S-028 do not entitle Vancocin to three years of exclusivity against generic competition, because the changes did not constitute “new conditions of use” within the meaning of section 505(v) of the FD&C Act.

#### **Attachments:**

- Appendix A: Labeling Changes
- Memorandum from Benjamin Lorenz, MD, to OCC and ORP (12/12/11)
- Memorandum from Benjamin Lorenz, MD, to OCC and ORP (12/15/11)
- Written Reply from Benjamin Lorenz, MD, to ORP Consult (4/9/12)