SUPPLEMENT ARTICLE

# Safety Analysis of Fidaxomicin in Comparison With Oral Vancomycin for *Clostridium difficile* Infections

**Karl Weiss,[1] Robin L. Allgren,[2] and Sarah Sellers[3]**

[1]Department of Infectious Diseases and Microbiology, Maisonneuve-Rosemont Hospital, Faculty of Medicine, University of Montreal, Quebec, Canada; [2]Breakthrough Bio Development, LLC, San Diego, California, and [3]q-Vigilance, LLC, Barrington, Illinois

**Fidaxomicin is a novel macrocyclic antibiotic recently approved by the US Food and Drug Administration for the treatment of *Clostridium difficile*–associated diarrhea in adults. We reviewed safety data from nonclinical studies and clinical trials (phases 1, 2A, and 3) with fidaxomicin. In nonclinical studies, fidaxomicin was administered orally at approximately 1 g/kg/d to dogs for up to 3 months with no significant target-organ toxicities observed. A total of 728 adults have received oral fidaxomicin in clinical trials to date: 116 healthy volunteers and 612 patients with *C. difficile* infection. In phase 3 clinical trials, fidaxomicin was well tolerated, with a safety profile comparable with oral vancomycin. There were no differences in the incidence of death or serious adverse events between the 2 drugs. Fidaxomicin appears to be well tolerated. Continued monitoring of adverse events in the postmarketing setting will provide additional information about the full safety profile of fidaxomicin.**

*Clostridium difficile* was recognized as the causative agent for antibiotic-associated colitis in 1978 [1], first observed in conjunction with clindamycin treatment [2]. Since then, *C. difficile* infection (CDI) has become an increasingly challenging nosocomial infection with severe medical consequences [3–6].

Hamster animal models showed some protective and beneficial effect from oral vancomycin, which quickly became the treatment drug of choice [7, 8]. However, the use of all vancomycin formulations (parvules and intravenous vancomycin used orally) had to be limited either because of its high price (parvules) or to curtail the potential risk for the emergence of vancomycin-resistant enterococci (VRE) [9]. In 1995, the Centers for Disease Control and Prevention recommended that vancomycin not be used orally for CDI in hospital settings as a strategy to prevent the emergence of VRE and vancomycin intermediate *Staphylococcus aureus*.

Prior to the approval of fidaxomicin, oral vancomycin was the only agent approved by the US Food and Drug Administration (FDA) for the treatment of antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Metronidazole was subsequently used off-label and, as a much less expensive alternative, became the de facto first-line treatment for mild to moderate cases of CDI [8, 10]. Other antibiotics have been tried in the past (fusidic acid, bacitracin, rifaximin, and nitazoxanide), but only limited clinical data are available for the treatment of CDI [11]. Thus, there has been a need for new therapies to treat this challenging disease.

Ideally, drugs against *C. difficile* should be minimally absorbed, remain in the intestinal lumen, and have a narrow spectrum of activity, preserving the normal microbiota of the gut.

Fidaxomicin has a narrow-spectrum antibacterial profile, with potent bactericidal activity specifically

Correspondence: Karl Weiss, MD, FRCPC, Maisonneuve-Rosemont Hospital, 5415 L'Assomption, Montreal, QC, Canada H1T 2M4 (weisscan@aol.com).

**Clinical Infectious Diseases 2012;55(S2):S110–15**



DOI: 10.1093/cid/cis390

against *C. difficile*. It displays moderate in vitro activity against some Gram-positive bacteria (*S. aureus* and *Enterococcus* spp.) and is inactive against Gram-negative organisms and yeast. Fidaxomicin is minimally absorbed from the gastrointestinal (GI) tract, with plasma concentrations in the nanogram-per-milliliter range after oral dosing.

In 2 phase 3 trials, fidaxomicin demonstrated noninferiority to vancomycin for clinical response in the treatment of CDI and superiority to vancomycin for sustained clinical response (cure without recurrence during the 30-day follow-up period). The efficacy results are presented in detail elsewhere [12, 13]. The safety results from nonclinical and clinical studies are summarized in the following sections.

## NONCLINICAL SAFETY STUDIES

A standard battery of nonclinical studies was conducted to assess the safety of fidaxomicin, including general toxicity (acute and repeated dose for up to 3 months), safety pharmacology, reproductive toxicity, and genotoxicity studies [13].

For a single intravenous fidaxomicin dose in rats, the 50% lethal dose was approximately 200 mg/kg and the no observed adverse effect level (NOAEL) was determined to be 62.5 mg/kg; at this NOAEL dose, the peak plasma level of fidaxomicin was 3000–10 200 ng/mL, which is at least 300-fold higher than the maximum concentration observed in humans. The toxicity of fidaxomicin was also evaluated in a repeated-dose setting in rats and monkeys at oral doses up to 90 mg/kg/d for 28 days; there were no drug-related deaths or effects on clinical observations. In a 3-month study in dogs, the NOAEL oral dose was the highest dose of 9.6 g/d (equivalent to 94–1160 mg/kg/d). Although some emesis and soft stools were observed at the highest doses in this study, these were attributed to the very large doses delivered (5%–7% of daily food intake). They were not exacerbated with continued dosing and were not associated with changes in food consumption or weight gain between groups or with histological changes. This indicates that high fecal levels of fidaxomicin (up to milligram-per-gram levels) are not associated with GI toxicity. None of these studies revealed evidence of toxicity to the bone marrow/hematopoietic system, liver, kidney, or other target organ.

The hERG channel, a potassium ion channel, mediates the repolarizing current in the cardiac action potential. When this channel's ability to conduct electrical current across the cell membrane is inhibited or compromised, by either drugs or rare mutations in some families, it can result in a potentially fatal disorder called long-QT syndrome. An in vitro assay has been established to screen drugs for hERG inhibition.

In vitro, neither fidaxomicin nor its main metabolite OP-1118 had an inhibitory effect on the hERG channel current (half maximal inhibitory concentration greater than the highest nominal dose tested of 10 μg/mL).

The potential for reproductive toxicity was assessed in a fertility study in rats and embryo-fetal development studies in rats and rabbits. Fidaxomicin did not affect the fertility of male and female rats at intravenous doses of 6.3 mg/kg, resulting in systemic exposure approximately 100 times that in humans. Fidaxomicin at the highest dose tested in rats (15 mg/kg/d) and rabbits (7.5 mg/kg/d) exhibited no maternal, reproductive, or embryo-fetal developmental toxicity.

The genotoxicity of fidaxomicin was assessed in in vitro (bacterial reverse mutation and chromosomal aberration assays) and in vivo (rat micronucleus assay) studies. Additionally, the main active metabolite OP-1118 was evaluated for genotoxicity in vitro (bacterial reverse mutation and chromosomal aberration assays). Overall, results from genotoxicity tests showed that fidaxomicin is not expected to be genotoxic in humans. Long-term carcinogenicity studies have not been conducted to evaluate the carcinogenic potential of fidaxomicin.

## SAFETY PROFILE IN CLINICAL TRIALS

During the clinical development of fidaxomicin, 728 subjects received fidaxomicin: 116 healthy adult volunteers in phase 1 studies and 612 adults with CDI in phase 2A and 3 studies. In the phase 1 and 2A studies, subjects were exposed to doses of fidaxomicin ranging 100–450 mg. No significant dose-related adverse events (AEs) were observed [14, 15].

The safety and efficacy of fidaxomicin were compared with oral vancomycin in 2 randomized, double-blinded pivotal phase 3 studies. One was performed in North America [12], and the other was performed in both North America and Europe [13]. In both phase 3 studies, fidaxomicin was administered orally at 200 mg every 12 hours for 10 days, and vancomycin was administered orally at 125 mg every 6 hours for 10 days (the currently recommended dose for nonfulminant disease). In these studies, 564 subjects with CDI were treated with fidaxomicin and 583 were treated with vancomycin, respectively. Overall, 86.7% of subjects completed a full course of treatment.

Of the 1147 subjects evaluable for the pooled phase 3 safety analysis, 567 (49.4%) were aged ≥65 years (272 treated with fidaxomicin and 295 treated with vancomycin), reflecting that the elderly are disproportionately affected by CDI. Subjects were mainly white (90%), female (58%), and in-patients (64%). Many subjects enrolled in the phase 3 program were acutely ill, with concomitant acute and chronic medical conditions in addition to CDI.

In these clinical studies, the safety profile of fidaxomicin was comparable with that of the active comparator vancomycin. For example, the total number of deaths in the phase 3 trials

was similar for fidaxomicin (36 of 564; 6.4%) and vancomycin (38 of 583; 6.5%; $P$ = not significant). None of these deaths was believed to be due to study drug toxicity, but they were attributed to the subject's significant underlying morbidities. Nine of the deaths were deemed possibly related to progression of the underlying CDI: 5 for fidaxomicin and 4 for vancomycin (5 men, 4 women; mean days on therapy, 6.78). In terms of any serious AEs (SAEs) or general AEs, the overall rates also were similar (Table 1). The vast majority of all events were rated as not related to study drug by the investigators.

Rates for discontinuation of dosing due to an AE were also comparable for both drugs in the phase 3 trials. There were 33 of 564 (5.9%) and 40 of 583 (6.9%) subjects in the fidaxomicin and vancomycin arms, respectively, who stopped their treatment due to an AE ($P$ = .48). Vomiting was the most frequent AE leading to study drug discontinuation. This occurred for 0.5% of subjects in both treatment groups [16].

### GI Safety

Because the majority of fidaxomicin remains in the intestinal lumen and exerts its activity there, GI AEs in the fidaxomicin phase 3 studies were evaluated closely. In the phase 3 studies, the number of overall GI AEs and SAEs was similar between the fidaxomicin and vancomycin groups. Slightly more GI AEs led to discontinuation from the study in the fidaxomicin group than in the vancomycin group (2.3% vs 1.4%; $P$ = .24), but deaths due to a GI AE tended to occur less frequently in the fidaxomicin group than the vancomycin group (0.5% vs 1.0%; $P$ = .51).

Some form of GI bleeding occurred in 23 fidaxomicin-treated patients (23 of 564; 4.1%) and 18 vancomycin-treated patients (18 of 583; 3.1%; $P$ = .37). All GI bleeding events in fidaxomicin subjects were deemed not related or unlikely related to the drug by the investigators. Also, many of these subjects had other risk factors for GI bleeding, such as recent bowel surgery, coagulopathies, or concomitant medications with anticoagulant properties. For fidaxomicin subjects, the early GI bleeding events tended to be mild self-limited events (such as a single bloody bowel movement or intermittent bleeding from preexisting rectal hemorrhoids) not requiring intervention. Fidaxomicin was not associated with an increase in bleeding events in other (non-GI) organ systems.

Three patients in the fidaxomicin arm developed megacolon, an unfortunate complication of CDI. One subject received only 2 doses before his condition worsened. For the 2 other subjects, megacolon was diagnosed with a treatment failure on days 3 and 6 of therapy, respectively. One vancomycin subject presented with a large-intestine perforation on day 31 and was found to have toxic megacolon during colectomy.

**Table 1. Adverse Events in Phase 3 Trials**

| Subjects With ≥1 AE | Fidaxomicin, 400 mg (n = 564), No. (%) | Vancomycin, 500 mg (n = 583), No. (%) |
|---|---|---|
| Any AE | 385 (68.3) | 382 (65.5) |
| AEs by severity | | |
| Mild | 160 (28.4) | 171 (29.3) |
| Moderate | 117 (20.7) | 113 (19.4) |
| Severe | 108 (19.1) | 98 (16.8) |
| AEs leading to discontinuation of study drug | 33 (5.9) | 40 (6.9) |
| AEs leading to dose modification or use of concomitant medication | 2 (0.4) | 8 (1.4) |
| Serious AEs | 145 (25.7) | 135 (23.2) |
| AEs resulting in death | 36 (6.4) | 38 (6.5) |

Abbreviation: AE, adverse event.

### Hematologic Safety

Anemia was reported in 2% of both fidaxomicin and vancomycin subjects. Leukopenia (eg, decreases in white blood cell counts or neutrophils) were observed in 14 of 564 (2.5%) fidaxomicin subjects and 6 of 583 (1.0%) vancomycin subjects ($P$ = .06). There was no apparent explanation for this finding except that more patients received antineoplastic or immunomodulating agents in the fidaxomicin group (11.9% vs 8.2%; $P$ = .04) [13]. Nearly all these reported events of leukopenia occurred in subjects with underlying hematologic malignancies, recent bone marrow transplant, and/or recent chemotherapy. No specific bone marrow toxicity was observed with fidaxomicin in the nonclinical studies [13]. The main clinical concern regarding leukopenia is that it could lead to an increased incidence of serious infections. However, it should also be noted that no overall increased incidence of infections with fidaxomicin vs vancomycin was observed in the phase 3 studies (22.9% vs 20.8%, respectively). The incidence of infections resulting in death was 2.0% for fidaxomicin subjects and 1.9% for vancomycin subjects. No adverse effect on platelet counts was observed in nonclinical or clinical studies.

### Cardiac Safety

Electrocardiograms (ECGs) were obtained before the first dose and at the end of therapy. No significant changes in ECGs were observed during the study period. There were no significant corrected QT (QTc) interval modifications for either group in the phase 3 studies (Table 2). There was no association between QTc interval prolongation and increased fidaxomicin level. One patient receiving oral vancomycin in a phase 3 trial developed torsades de pointes. Deaths due to cardiac events occurred in 0.4% of fidaxomicin subjects and 1.2% of vancomycin subjects ($P$ = .18). In a subgroup analysis with high plasma levels (fidaxomicin plus OP–1118 levels

**Table 2. Summary of 12-Lead Electrocardiogram Corrected QT Interval Results (Bazett's and Fridericia's corrections): Phase 3 Studies**

| QTc intervals | Bazett's | | Fridericia's | |
|---|---|---|---|---|
| | Fidaxomicin (n = 501), No (%) | Vancomycin (n = 503), No. (%) | Fidaxomicin (n = 501), No. (%) | Vancomycin (n = 503), No. (%) |
| Changes in QTc interval from baseline (ms) | | | | |
| >30 | 42 (8.7) | 32 (6.6) | 37 (7.7) | 35 (7.2) |
| >60 | 6 (1.2) | 6 (1.2) | 6 (1.2) | 5 (1.0) |
| QTc interval at end of study (ms) | | | | |
| >450 | 96 (19.2) | 109 (21.7) | 43 (8.6) | 54 (10.7) |
| >480 | 26 (5.2) | 34 (6.8) | 13 (2.6) | 16 (3.2) |
| >500 | 12 (2.4) | 14 (2.8) | 7 (1.4) | 11 (2.2) |

Only subjects with both baseline and end-of-study electrocardiogram values are included in this evaluation.

Abbreviation: QTc, corrected QT.

≥150 ng/mL), there was no association between QTc interval prolongation and drug levels.

### Hepatic Safety

In the phase 3 clinical studies, the incidence of AEs involving abnormal liver function test (LFT) results was similar between fidaxomicin and vancomycin (3.2% vs 2.6%; $P = .53$). No significant changes in mean LFT results were observed in either group (Table 3). The numbers of subjects with normal LFT results at baseline but a later LFT result at least 3 times the upper limit of normal (ULN) were 6 for fidaxomicin and 5 for vancomycin. No subject in either group had an increase in aspartate or alanine aminotransferase level to >3 times ULN with an increase in bilirubin level >2 times ULN. Adverse events were also examined for subjects with and without abnormal LFT results at baseline. The overall incidence of AEs was similar for fidaxomicin- and vancomycin-treated subjects with and without these abnormal laboratory parameters.

### Use in Renal Impairment

No specific safety studies have been carried out to date with fidaxomicin in subjects with renal or hepatic impairment. However, 48% of subjects in the phase 3 studies had renal insufficiency at baseline, and the safety of fidaxomicin was examined in subgroups of subjects who had varying degrees of renal insufficiency based on estimated creatinine clearance and characterized as either mild (51–79 mL/min), moderate (31–50 mL/min), or severe (≤30 mL/min). No clinically significant differences in the incidence of AEs between fidaxomicin and vancomycin subjects were observed within subpopulations with mild, moderate, or severe renal insufficiency.

**Table 3. Summary Statistics for Changes in Liver Function Parameters Between Baseline and End of Therapy: Phase 3 Studies**

| Parameter | Fidaxomicin 400 mg (n = 564) | Vancomycin 500 mg (n = 583) |
|---|---|---|
| ALT (U/L) | | |
| Patients, No. | 482 | 478 |
| Mean change | 6.1 | −0.3 |
| SD | 48.62 | 71.52 |
| Median change | 2 | 2 |
| Alkaline phosphatase (U/L) | | |
| Patients, No. | 502 | 506 |
| Mean change | 3 | 2.7 |
| SD | 59.07 | 47.19 |
| Median change | −1 | 1 |
| AST (U/L) | | |
| Patients, No. | 473 | 459 |
| Mean change | 3 | −4.5 |
| SD | 24.26 | 136.48 |
| Median change | 2 | 2 |
| Bilirubin (mmol/L) | | |
| Patients, No. | 485 | 481 |
| Mean change | −0.65 | −0.92 |
| SD | 5.17 | 15.19 |
| Median change | 0 | 0 |
| Direct bilirubin (mmol/L) | | |
| Patients, No. | 443 | 433 |
| Mean change | −0.33 | −0.47 |
| SD | 2.88 | 7.51 |
| Median change | 0 | 0 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation.

### Use in Pregnancy

To date, there are no meaningful data available for fidaxomicin use during pregnancy in humans. One woman with B-cell lymphoma in a phase 3 study receiving fidaxomicin and also receiving numerous other agents (including methotrexate and vincristine) had a multiple-birth pregnancy. Her pregnancy test was negative at enrollment and became positive on day 25. She delivered 3 live and 1 dead fetuses; 1 female fetus was found to have a cleft palate.

## DISCUSSION

In phase 3 trials, the overall safety profile of fidaxomicin was comparable with that of oral vancomycin. There was no difference in the incidence of deaths or SAEs between the fidaxomicin and vancomycin arms. There was a numerical imbalance in AEs related to GI hemorrhage (4.1% vs 3.1%) and leukopenia (4.1% vs 1.7%) between the fidaxomicin and vancomycin

groups, but no causal relationship between fidaxomicin and these events could be established.

The oral formulation of vancomycin has been on the market for >2 decades. Vancomycin can be administered to children and pregnant women, and its long-term administration as a therapy for recurrent CDI has not been linked to any significant safety issues, with a long-term safety track record unmatched by other drugs targeting CDI. Overall, the safety profile of vancomycin in CDI is consistent with the agent's limited solubility and minimal systemic exposure after oral administration. However, absorption may be facilitated by an inflamed gut, with increased potential for systemic side effects [17]. Recently, a maculopapular rash induced by oral vancomycin has been reported [18].

The lower cost of metronidazole in comparison to vancomycin, the similar clinical effectiveness for mild to moderate disease, and the threat of VRE has favored the use of the former as first-line therapy for this type of patient. Oral metronidazole absorption is very high and potentially can lead to more systemic side effects. Metronidazole has been linked to several safety issues, including peripheral and optic neuropathy [19, 20], and frequent less serious side effects (nausea, taste disturbance, and headache).

Metronidazole is not approved by the FDA for the treatment of CDI. Drugs such as warfarin and lithium are known to interact, and alcohol must be avoided. The clinical efficacy of metronidazole may be limited for more severe cases and for relapses [10].

*Clostridium difficile* infection is a growing concern for elderly frail patients who are disproportionately affected by the disease and its related morbidity and mortality [6]. Antibiotic stewardship is an interesting option to control CDI but has many limitations [21]. A bundle approach in terms of infection control can have a substantial impact on CDI rates but would not eliminate the issue [22]. Until recently, a limited number of therapeutic options were available [23].

The arrival of fidaxomicin represents a major addition to the CDI treatment armamentarium, a novel agent with a safety profile comparable with vancomycin in clinical trials. As with all new drug introductions and in particular with novel drugs, careful and continuous surveillance and monitoring in the postmarketing setting will augment the present premarketing safety experience and contribute to further understanding of the safety of fidaxomicin during routine clinical use.

## Notes

***Supplement sponsorship.*** This article was published as part of a supplement entitled "Fidaxomicin and the Evolving Approach to the Treatment of *Clostridium difficile* Infection," sponsored by Optimer Pharmaceuticals, Inc.

***Potential conflicts of interest.*** K. W. received research grants from Health-Canada, Valorisation Recherche Quebec, Abbott, Bayer, Bristol-Myers-Squibb, Genzyme Corp, GlaxoSmithKline, Optimer, Pharma, Pfizer, Roche, and Theravance. R .L. A. and S. S. are paid consultants to Optimer Pharmaceuticals, Inc, regarding pharmacovigilance and pharmacoepidemiology, respectively.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## References

1. Bartlett JG, Chang TW, Gurwith M, Gorbach SL, Onderdonk AB. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. N Engl J Med **1978**; 298:531–4.
2. Tedesco FL, Barton RW, Alpers DH. Clindamycin-associated colitis: a prospective study. Ann Intern Med **1974**; 81:429–33.
3. McDonald LC, Owings M, Jernigan DB. *Clostridium difficile* in patients discharged from US short-stay hospitals, 1996–2003. Emerg Infect Dis **2006**; 12:409–15.
4. Kyne L, Hamel MB, Polavaram L, Kelly CP. Health-care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. Clin Infect Dis **2002**; 34:346–53.
5. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*–associated diarrhea with high morbidity and mortality. N Engl J Med **2005**; 353:2442–9.
6. Zilberberg MA, Shorr AF, Kollef M. Increase in adult *Clostridium difficile*–related hospitalizations and case-fatality rate, United States 2000–2005. Emerg Infect Dis **2008**; 14:929–31.
7. Browne RA, Fekety R Jr, Silva J, Boyd DI, Work CO, Abrams GD. The protective effect of vancomycin on clindamycin-induced colitis in hamsters. Johns Hopkins Med J **1977**; 141:183–92.
8. Bartlett JG. The case for vancomycin as the preferred drug for treatment of *Clostridium difficile* infection. Clin Infect Dis **2008**; 46:1489–92.
9. Gerding DN. Is there a relationship between vancomycin-resistant enterococcal infection and *Clostridium difficile* infection? Clin Infect Dis **1997**; 25(Suppl 2):S206–10.
10. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*–associated diarrhea stratified by disease severity. Clin Infect Dis **2007**; 45:302–7.
11. Wenisch C, Parschalk B, Hasenhündl M, Hirschl AM, Graninger W. Comparison of vancomycin, teicoplanin, metronidazole and fusidic acid for the treatment of *Clostridium difficile*–associated diarrhea. Clin Infect Dis **1996**; 22:813–8.
12. Louie TJ, Miller MA, Mullane KM, et al. OPT-80-003 Clinical Study Group. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med **2011**; 364:422–31.
13. Anti-Infective Drugs Advisory Committee. Dificid™ (fidaxomicin tablets) for the treatment of *Clostridium difficile* infection (CDI), also known as *Clostridium difficile*–associated diarrhea (CDAD), and for reducing the risk of recurrence when used for treatment of initial CDI. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM249354.pdf. Accessed 11 November 2011.
14. Shue YK, Sears PS, Shange S, et al. Safety, tolerance, and pharmacokinetic studies of OPT-80 in healthy volunteers following single and multiple oral doses. Antimicrob Agents Chemother **2008**; 52:1391–5.
15. Louie T, Miller M, Donskey C, Mullane K, Goldstein EJC. Clinical outcomes, safety, and pharmacokinetics of OPT-80 in a phase 2 trial with patients with *Clostridium difficile* infection. Antimicrob Agents Chemother **2009**; 53:223–8.
16. Gorbach S, Weiss K, Sears P, Pullman J. Safety of fidaxomicin versus vancomycin in treatment of *Clostridium difficile* infection [poster L1-1640]. In: Program and abstracts of the 49th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington, DC: ICAAC, 2009.

17. Aradhyula S, Manian FA, Hafidh SA, Bhutto SS, Alpert MA. Significant absorption of oral vancomycin in a patient with *Clostridium difficile* colitis and normal renal function. South Med J **2006**; 99:518–20.
18. Osawa R, Kaka AS. Maculopapular rash induced by oral vancomycin. Clin Infect Dis **2008**; 47:860–61.
19. Duffy LF, Daum F, Fisher SE, et al. Peripheral neuropathy in Crohn's disease patients treated with metronidazole. Gastroenterology **1985**; 88:681–4.
20. McGrath NM, Kent-Smith B, Sharp DM. Reversible optic neuropathy due to metronidazole. Clin Experiment Ophthalmol **2007**; 35:585–6.
21. Owens RC, Donskey CJ, Gaynes RP, Loo VG, Muto CA. Antimicrobial-associated risk factors for *Clostridium difficile* infection. Clin Infect Dis **2008**; 46(Suppl 1):S19–31.
22. Weiss K, Boisvert A, Chagnon M, et al. Multipronged intervention strategy to control an outbreak of *Clostridium difficile* infection (CDI) and its impact on the rates of CDI from 2002 to 2007. Infect Control Hosp Epidemiol **2009**; 30:156–62.
23. ViroPharma Inc. Vancocin HCl capsules (vancomycin hydrochloride capsules, USP) [prescribing information]. Available at: http://www.vancocin.com/~/media/Vancocin/Files/Vancocin_PI.ashx. Accessed 14 November 2011.