Drug Use Research & Management Program
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Month/Year of Review: April 2012
Generic Name: Fidaxomicin
Dossier received: Yes

End date of literature search: February 2012
Brand Name (Manufacturer): Dificid® (Optimer Pharmaceuticals)
Comparator Therapies: Vancomycin, Metronidazole

Executive Summary:

FDA Approved Indications: Fidaxomicin is a macrolide antibacterial drug indicated for treatment of *Clostridium difficile* associated diarrhea (CDAD) in adults ≥ 18 years of age.[1]

Summary: *Clostridium difficile* infection (CDI) is a growing health care problem and a serious healthcare-associated infection that has continued to emerge over the past three decades. Current epidemic rates of CDI in the United States, Canada, and Europe have been associated with a hyper-virulent strain (BI/NAP1/027). This strain is associated with increased toxin production and increased mortality and morbidity.[2] Previously thought to be a disease of hospitalized patients, community-associated CDI is increasingly being recognized in children and adults with similar risk factors. The evidence used for many of the current guidelines is weak due to small studies often with a high risk of bias and frequently excluding patients with severe disease. The relative burden of CDI in nonhospital health-care settings remains unknown. In May, 2011, the FDA approved fidaxomicin for the treatment of CDAD. In December 2011, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review (CER) on the effectiveness of early diagnosis, prevention, and treatment of CDI that was updated to include one of the approval studies of fidaxomicin that was published at the time as well as the increasing amount of published treatment studies coinciding with the increased incidence and severity of CDI.[3] Fidaxomicin is a new antibacterial drug indicated primary for treatment of *Clostridium difficile*.

The authors of the AHRQ CER concluded that no antimicrobial is clearly superior for the initial cure of CDI. There was moderate-strength evidence that fidaxomicin and vancomycin did not differ for the outcome of initial cure but that recurrence was less frequent with fidaxomicin based on one high-quality study.[3] There was also moderate-strength evidence that outcomes did not differ between metronidazole and vancomycin in nonsevere disease and insufficient evidence to evaluate a difference in severe CDI. There was insufficient evidence to compare the risks of any particular antimicrobial with another one. Although guidelines recommend vancomycin as first line in severe disease, there is insufficient evidence to support that it is generally superior to metronidazole. However, there also appears to be clinical consensus to treat mild to moderate CDI with metronidazole, in part because of the concern that overuse of vancomycin may contribute to increasing pathogen resistance and cost considerations.[3]

Conclusions:
There is moderate strength evidence that there is no difference in clinical cure rate between fidaxomicin, vancomycin, and metronidazole. There is moderate strength evidence that recurrence occurs less frequently with fidaxomicin versus vancomycin. Current guidelines recommend metronidazole and vancomycin as the standard treatment options for *Clostridium difficile* infection.[7] However, a recent Cochrane review of clinical trials showed that there is no strong evidence to support current recommendations made by the guidelines.[6] Further head-to-head studies are needed in severe disease and to compare directly fidaxomicin to metronidazole. Therapy with fidaxomicin may provide value to patients at high risk of rehospitalization due to recurrence or other serious complications. It is still unknown how to best identify this patient population.

Recommendations:
- Recommend making fidaxomicin a non-preferred antimicrobial for CDI and requiring a documented trial of appropriate therapy of vancomycin (125mg oral four times daily) or metronidazole (500mg orally three times daily) for first recurrence or contraindication to therapy and excluding use of fidaxomicin in patients with severe, complicated CDAD (life-threatening or fulminant infection or toxic megacolon).
- Recommend adding oral metronidazole and oral vancomycin as preferred agents on the PDL for the treatment of CDI.
- Consider requiring metronidazole as first line therapy for mild CDAD in non-hospitalized patients.

Efficacy: Two phase III randomized, controlled, double-blind, identically designed clinical trials compared the efficacy of fidaxomicin 200 mg twice daily versus oral vancomycin 125 mg four times daily for 10 days in adult patients with a diagnosis of CDAD and history of ≤ 1 recurrence.[4, 5] The primary endpoint in both trials was the clinical response rate at the end of therapy. One trial was conducted in North America[4] and the second trial in North America and Europe.[5] Both trials demonstrated that fidaxomicin was noninferior to vancomycin in clinical cure rate with 88.2% of patients on fidaxomicin achieving clinical cure compared to 85.8% on vancomycin in one trial (RR 0.97 95% CI 0.91 to 1.04)[4] and 88% of fidaxomicin versus 87% vancomycin patients in the second trial (p=0.074).[5] Both trials also demonstrated a statistically significant difference in recurrence rates between the two groups. Recurrence rates were 15.4% for fidaxomicin versus 25.3% for vancomycin (p=0.005) in one trial and 12.7% for fidaxomicin versus 27% for vancomycin (p<0.001) in the second trial. However, in patients with the hyper-virulent strain, (approximately 40% of all isolates) there was no significant difference in recurrence rate between the two groups in either study.[4, 5] In a subgroup analysis, recurrence rates were significantly lower in fidaxomicin-treated patients who were >65 years old, had no prior episodes of CDAD, were not receiving concomitant antibiotics, and had a non-BI/NAP1/027 strain.

Safety: Rates of adverse and serious adverse events were similar in the fidaxomicin and vancomycin groups and both also had similar rates of discontinuations due to adverse events (5.9% in fidaxomicin compared to 6.9% for vancomycin group).[4,5] The most common adverse reactions associated with fidaxomicin treatment in clinical trials are nausea (11%), vomiting (7%), abdominal pain (6%), gastrointestinal hemorrhage (4%), anemia (2%), and neutropenia (2%).[1] Both the AHRQ review and a recent systematic review from the Cochrane Collaboration found that although harms were often not reported with sufficient detail to compare risks associated with the antibiotics, adverse events were infrequent and transient and were generally not serious.[3,6] The safety and effectiveness of fidaxomicin has not been studied in patients younger than 18 years.[1]

BACKGROUND/CURRENT LANDSCAPE/SUMMARY

The incidence, mortality, and medical care costs of CDIs have reached historic highs. From 2000 to 2009, the number of hospitalized patients with any CDI discharge diagnoses more than doubled, from approximately 139,000 to 336,000.[2] Strategies for prevention should be initiated to reduce the incidence of CDI as many of these infections can be prevented.[2] *C. difficile* generally occurs after exposure to broad-spectrum antibiotics, but any antibiotic that disrupts the normal flora of the gut can increase susceptibility.[7] A recent drug safety communication was released by the FDA, notifying the public that the use of stomach acid drugs such as proton pump inhibitors may also be associated with an increased risk of C. difficile associated diarrhea (CDAD).[8] They are also reviewing the risk of CDAD associated with histamine H2 receptor blockers.[8] Recurrence of CDI occurs in approximately 20% of patients. After two recurrences, the risk that additional episodes will occur increases to 65%.[7] The treatment goals for CDI include resolution of diarrhea and other signs and symptoms, lack of disease recurrence, avoidance of colectomy, and no other serious sequelae of disease.

Oral metronidazole and vancomycin are the antibiotics most often used to treat CDI. Guidelines from the Society for Healthcare Epidemiology of America (SHEA) and The Infectious Diseases Society of America (IDSA) were updated in 2010 (prior to fidoxamicin's FDA approval for CDAD) and recommend metronidazole for initial episodes of mild to moderate diseases and oral vancomycin as the drug of choice for severe disease, using changing creatinine values and an abnormally high white blood cell count to define severity.[7] The usual duration of therapy is 10 to 14 days, although no well-performed studies have established the potential advantage of shortening or lengthening the course. Comparative clinical trials demonstrated equivalent rates of clinical cure for the two agents, but metronidazole is preferred for initial disease due to concerns regarding the emergence of vancomycin resistance and costs.[3] Overall, previous systematic reviews have concluded there is insufficient or low-strength evidence for any outcomes evaluating efficacy in severe CDI as many studies excluded these patients, although consensus guidelines recommend vancomycin as first line in severe disease. The only comparative evidence for vancomycin versus metronidazole in severe disease comes from a per-protocol subgroup analysis of 69 patients in a single trial. Although there was a statistically significant difference favoring vancomycin in the per-protocol and modified intention-to-treat analysis, there was no significant difference using a strict intention-to-treat analysis.[3]

A recent Cochrane systemic review from the Cochrane Collaboration aimed to evaluate the efficacy of antibiotic therapy for CDAD.[7] Out of the 15 studies included, 12 were rated as having a high risk of bias. In 3 studies (n=335), no statistically significant difference was found between vancomycin and metronidazole for symptomatic cure of CDAD. Symptomatic cure was achieved in 79% of patients in vancomycin group compared to 71% in metronidazole group (RR 0.91; 95% CI: 0.81-1.03).[7] The authors concluded that due to small number of patients, poor methodological quality studies, and exclusion of severe disease, a recommendation to achieve overall goals could not be made. Also, there was no statistical difference in bacteriologic cure between metronidazole and vancomycin in one study with 62 patients.

Clinical pharmacology

Fidaxomicin is a bactericidal macrolide antibiotic, primarily active against *Clostridium difficile*. The drug works by inhibiting bacterial RNA polymerase which stops RNA synthesis during transcription phase of protein synthesis. [1]

Pharmacokinetics:

Fidaxomicin has poor permeability and solubility; therefore it is minimally absorbed from the gastrointestinal tract. The drug is metabolized via hydrolysis to an active metabolite OP-1118. No CYP enzymes were found to play significant role in the metabolism of fidaxomicin or formation of OP-1118. The drug is primarily excreted in feces. Fidaxomicin fecal concentrations are detected up to 5 days after treatment.[12] The drug dosing does not need to be adjusted for decreased renal function, as there is <1% renal elimination. The impact of hepatic impairment on pharmacokinetics of fidaxomicin has not been evaluated because hepatic metabolism is not significant.[1] Table 1 in Appendix 1 compares pharmacokinetic parameters of fidaxomicin with other treatments for CDI including metronidazole and oral vancomycin.

COMPERATIVE CLINICAL EFFICACY

Relevant Endpoints

Initial Cure
Recurrence
Mortality

Study Endpoints:

Primary: Clinical Cure (resolution of symptoms and no need for further treatment)
Secondary: Recurrence (diarrhea and a positive result on a stool toxin test within 4 weeks after treatment)
Global Cure (cure with no recurrence)

Evidence table

Ref./ Study Design	Drug Regimens	Patient Population	N[5]	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results[2] (CI, p-values)	ARR / NNH	Quality Rating[4]; Comments
Louie et al., Phase III, DB, RCT[4] Study 003	F:Fidaxomycin 200mg PO BID V:Vancomicin 125mg PO QID	Adults with acute symptoms of CDI and a positive result on a stool toxin test in Canada and the USA. Mean age: 61.6 Female 55.9%, Inpatient 59.4%, Mean number of unformed stools/day: 8.2 **Inclusion: criteria:** • ≥16 y.o, *C.difficile* diagnosis (> 3 unformed stools in 24 h prior randomization, presence o toxin A, or both in stool within 48 h of randomization). **Exclusion criteria:** • Life-threatening *C.dificile* infection, Toxic megacolon, History of UC, Crohn's disease, >1 *C.difficile* infection within 3 months, Use of drugs to control diarrhea or those that affect paristalsis.	F: 302 V: 327	Treatment: 10 days Follow up: 30 days	**Initial Clinical Cure** Clinical cure: F: 253 (88%) V: 265 (85%) RR 0.97 95% CI (0.91 to 1.04) **Clinical Recurrence:** F: 39 (15%) V: 67 (25%) RR 0.6 95% CI (0.41 to 0.87) P=0.005 **Global Cure:** F: 214 (74.6%) V: 198 (64.1%) RR 1.16 95% CI (1.15 to 2.34) P=0.006	NS ARR 9.9% NNT 10 ARR 10.5% NNT 9.5	All-Cause Mortality F: 16 (5.3%) V: 21 (6.5%) P=0.6122 Any serious adverse event: F: 25% V:24.1% P=0.852 No subjects discontinued the study as a result of intolerance or allergy to medications	NS NS	Good; Adequate allocation concealment; double blinding, partially ITT analysis Total withdrawals and dropouts: 33 (5%) Funded by Optimer Pharmaceuticals. Intention-to-treat analysis: modified (subjects withdrawing before treatment, had ≤3 bowel motions in 24 hours, or tested negative for C. difficile toxin were excluded) Other medication use that can cause diarrhea not reported at baseline. Patients were allowed to use opioids during hospital stay. Opioid doses used by both groups not reported.

Cornely, et al. Phase III, DB RCT, PG[5] Study: 004	F: Fidaxomicin 200mg PO BID V: Vancomycin 125mg PO QID	Adults with acute symptoms of CDI and a positive result on a stool toxin test in Europe, as well as in Canada and the USA. Mean age: 63, Female: 60.9% **Inclusion: criteria:** • ≥16 y.o, *C.difficile* diagnosis (> 3 unformed stools in 24 h prior randomization, presence of toxin A, or both in stool within 48 h of randomization). **Exclusion criteria:** • Life-threatening *C.dificile* infection, Toxic megacolon, History of UC, Crohn's disease, >1 *C.difficile* infection within 3 months, Use of drugs to control diarrhea or those that affect paristalsis.	F: 270 V: 265	Treatment: 10 days Follow up: 28 days after treatment	**Clinical Cure:** F: 221 (87.7%) V: 223 (86.8%) P=0.754 **Recurrence:** F: 28 (12.6%) V: 60 (27%) RR 0.5 *P*=0.0002 **Global cure**: F: 193 (76.6%) V: 163 (63.4%) RR 1.2 P=0.001	NS ARR 14.4% NNT 7 ARR 13.2% NNT 7	Serious adverse event: F: 70 (26.5%) V: 58 (22.3%) Adverse events leading to discontinuation: F: 16 (6.1%) V: 16 (6.2%)	NS NS	Fair; Adequate allocation concealment; double blinding, partially ITT analysis Total withdrawals and dropouts: 79 (15%) Funded by Optimer Pharmaceuticals. Intention-to-treat analysis: modified (subjects withdrawing before treatment, had ≤3 bowel motions in 24 hours, or tested negative for C. difficile toxin were excluded) Some regional differences in the characteristics and responses of patients

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover. OP=open label. [2]**Results abbreviations**: ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval. [3]**NNT/NNH** are reported only for statistically significant results [4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
CA= concomitant antibiotic, UC=ulcerative colitis, N[5]= number randomized, 6=data from modified intention-to-treat population.

Clinical Efficacy:

In one good quality study and one fair quality study, fidaxomicin was shown to be non-inferior to vancomycin though it was also shown to have significantly lower rates of recurrence and higher rates of global cure. Study 003 enrolled subjects in the US and Canada, while study 004 enrolled subjects in Canada, the US, and Europe. Patients with severe, complicated CDAD were excluded from the clinical trials. Clinical cure was the principal comparison outcome between two treatments.[9] Clinical cure was defined as three or less unformed stools for 2 consecutive days, with maintenance of resolution for the duration of therapy and no further requirement for therapy as of the second day after the end treatment (10days).[9] Results for trial (003) published by Louie et al., showed clinical cure rate in modified intent-to-treat (mITT) population at 88.2% (253/287) in fidaxomicin group compared to 85.8% (265/309) in vancomycin group (RR 0.97; 95% CI 0.91 to 1.04).[4] The lower boundary of the 97.5% confidence interval for the difference of cure rates was at -3.1% points; therefore fidaxomicin met the non-inferiority criteria. [9] The results from trial (004) showed that cure rate for fidaxomicin group was at 86% (217/253) compared to 85% (219/256) in vancomycin group, respectively.[5,9]

In Study 003, Subgroup analyses of the rates of clinical cure according to the patients' age, inpatient vs. outpatient status, prior occurrence, treatment for *C difficile* infection vs. no treatment within 24 hours before the start of the trial, no response vs. response to previous metronidazole therapy and use vs. nonuse of concomitant systemic antimicrobial therapy showed no significant differences between treatments. In trial 004, more patients who received concomitant antibiotics for other infections during the study treatment period achieved clinical cure with fidaxomicin than with vancomycin (90.2% in fidaxomicin vs. 73.3% in vancomycin; p=0.031). For the secondary endpoints of recurrence and sustained

response, fidaxomicin was statistically superior to vancomyin only for patients receiving no concomitant antibiotics during the study. A follow-up study combined the results of these trials to investigate the association between concomitant use of antibiotics (CA) and recurrence rates.[10] Analysis of the pooled phase III data, demonstrated that recurrence rates were lower when patients who required CA were given fidaxomicin; a higher rate was seen in patients on antibiotics historically associated with a high risk of CDI recurrence. Use of concomitant antibiotics and CDI treatment was associated with a lower cure rate, 80% in concomitant antibiotic users versus 93% of nonusers (*P*<0.001). Clinical cure rates in the PP analysis were 87% in concomitant antibiotic users and 93% in nonusers in the fidaxomicin group, and 77% in concomitant antibiotic users and 94% in nonusers in the vancomycin group.[10]

In study 003, there was no significant difference in mean days to resolution of diarrhea (Vancomycin median 3.3 days vs. Fidaxomicin 2.4 days; p=NS). And there was no significant difference in all-cause mortality (7% in vancomycin group vs. 5% in fidaxomicin group). The majority of patients enrolled in the clinical trials were inpatients and the BI/NAP1/027 strain comprised approximately 40% of all isolates. Around 40% of patients in the 003 trial and 30% in the 004 trial were outpatient. In patients with the hyper-virulent strain, there was no significant difference in recurrence rate in either study (fidaxomicin 27.1% vs. vancomycin 20.9%, p=0.42 in study 003, and 22.2% vs. 38%, p=0.079 in study 004).

Safety:

Adverse events were not significantly different between fidaxomicin and vancomycin groups. The occurrence of any serious adverse event was at 25% in fidaxomicin group compared to 24.1% in vancomycin group in study 003.[1,4] However, the fidaxomicin group had significantly more adverse events related to laboratory tests at 4.7% compared to vancomycin group at 1.2% (P=0.01). According to a FDA medical review, which looked at data from both phase III trials, serious adverse events occurred at rate of 25.7% in fidaxomicin treated individuals compared to 23.2% in vancomycin patients.[9] The three severe adverse effects that occurred more frequently in fidaxomicin group were gastrointestinal hemorrhage, megacolon and decrease in WBC counts. Around 3 patients developed megacolon in fidaxomicin group compared to none in vancomycin. The most common adverse events reported in both groups during phase III trials were nausea, vomiting, hypokalemia, headache, abdominal pain, diarrhea, constipation and pyrexia. The incidence of abdominal pain, constipation and hypokalemia was higher in fidaxomicin group. In addition, the rate of deaths in both phase III trials was similar for both groups. Around 36 people died in fidaxomicin group (6.4%) compared to 38 in vancomycin group (6.5%).[9]

Table 3. Adverse event comparison between fidaxomicin and vancomycin[1,9]

	Fidaxomicin (N=564)	Vancomycin (N=583)
Anemia	14 (2.5%)	12 (2.1%)
Neutropenia	14 (2.5%)	6 (1.0%)
Lymphopenia	11 (1.9%)	5 (0.9%)
Gastrointestinal hemorrhage	20 (3.5%)	12 (2.1%)
Nausea	62 (11%)	66 (11.3%)
Vomiting	41 (7.3%)	37 (6.3%)
Constipation	25 (4.4%)	12 (2.1%)
Diarrhea	28 (5%)	39 (6.7%)
Abdominal pain	33 (5.9%)	23 (3.9%)
Hypokalemia	47 (8.3%)	38 (6.5%)
Headache	37 (6.6%)	27 (4.6%)
Pyrexia	24 (4.3%)	31 (5.3%)

Precautions/Contraindications:
Currently there are no contraindications listed for fidaxomicin. The drug should not be used for systemic infections. Also, fidaxomicin should be only used for treatment of *C.difficile* associated infection in order to avoid bacteria resistance. [1]

Tolerability:
According to the FDA review, a total of 57 patients (10.1%) in fidaxomicin group and 58 patients (9.9%) in vancomycin group were withdrawn from phase III trials due to treatment failure or adverse events.[9] During treatment phase in both phase III trials there were 22 patients (3.9%) in fidaxomicin group and 36 patients (6.2%) in vancomycin group who stopped the drug due to adverse event. Around 22 patients (3.9%) taking fidaxomicin and 17 patients (2.9%) taking vancomycin had discontinued therapy during follow-up in both phase III trials. [9]

Pregnancy/Lactation rating:
Pregnancy category B based from animal studies. However, no studies in pregnant women were done. Therefore, the manufacturer recommends using the drug during pregnancy only if clearly needed. It is unknown if fidaxomicin is excreted in milk. Nursing women should use the drug with caution. [1]

Dose Index (efficacy/toxic):
The greatest efficacy in CDI treatment was established with fidaxomicin 200mg twice daily in phase II trial. No drug-related adverse effects were seen in dogs dosed with fidaxomicin tablets at 9600 mg/day. [9]

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for [Fidaxomicin]	None Identified	None Identified	None identified	None Identified	Filgrastim
LA/SA for [Dificid]	None Identified	None Identified	None identified	None Identified	Difiram, Difil-G, Dilaudid, Dilacor XR, Denavir, Dynacin, Diflosid, Digifab,

Allergies/Interactions:

Drug-Drug: Fidaxomicin is poorly absorbed and metabolized primarily by esterase to an active metabolite. There are no known drugs in the market that cause clinically relevant drug interactions by inhibiting esterases; therefore the inhibition of metabolism of fidaxomicin is not anticipated. Fidaxomicin and its main metabolite are substrates of p-glycoprotein. Based on in vivo studies it was concluded that no dose adjustment is warranted when fidaxomicin is co-administered with substrates of p-glycoprotein or CYP enzymes. Also, fidaxomicin may be co-administered with p-glycoprotein inhibitors without dose adjustment. [1]
Food-Drug: Fidaxomicin may be taken with or without food. [1]

Dose and Availability: [1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
200mg	Tablet	Oral	Twice daily	None	None	Not recommended	Adjustment not recommended	None

References:

1. Dificid® Prescribing Information. Optimer Pharmaceuticals, Inc. San Diego, CA.
2. McDonald L, et al. Vital Signs : Preventing Clostridium difficile Infections. Centers for Disease Control MMWR 2012;61:1-6.
3. Butler M, Bliss D, Drekonja D, Filice G, Rector T, MacDonald R, Wilt T. Effectiveness of Early Diagnosis, Prevention, and Treatment of Clostridium difficile Infection. Comparative Effectiveness Review No. 31 (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-02-0009.) AHRQ Publication No. 11(12)-EHC051-EF. Rockville, MD. Agency for Healthcare Research and Quality. December 2011
4. Louie T.J., Miller M.A., Mullane K.M., Weiss K., Lentnek A., Golan Y., Gorbach S., Sears P., Shue Y.K., Fidaxomicin versus vancomycin for *Clostridium difficile*. NEJM, 2011; 364: 422-31
5. Cornely Ol, Crook Dr., Esposito R., Poirier A., Somero M., Sears P., et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomized controlled trial. Lancet Infect Dis. Available online 7 February 2012, ISSN 1473-3099, 10.1016/S1473-3099(11)70374-7.
6. 8 .Nelson RL, Kelsey P, Leeman H,Meardon N, Patel H, Paul K, Rees R, Taylor B,Wood E,Malakun R. Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No.: CD004610. DOI: 10.1002/14651858.CD004610.pub4.
7. Cohen S.H., Gerding D.N., Johnson S., Kelly C.P., Loo V.G. , McDonald C.L. , Pepin J., Wilcox M.H., 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). *Infection Control and Hospital Epidemiology*, 2010; 31(5):431-455
8. FDA Drug Safety Communication: Clostridium Difficile-Associated Diarrhea (CDAD) Can be Associated with stomach acid drugs. [Posted 02/08/12]. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm290838.htm
9. Center for drug evaluation and research. Medical Review. Application Number 201699Orig1s000. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201699Orig1s000TOC.cfm
10. Mullane Kl, Miller M., Weiss K., Lentnek A., Golan Y., et al. Efficacy of Fidaxomicin Versus Vancomycin as Therapy for Clostridium difficile Infection in Individuals Taking Concomitant Antibiotics for Other Concurrent Infections. Clinical Infectious Diseases. 2011;53(5):440-447
11. Flagyl. In: DrugDex [Micromedex Online]. Greenwood Village, CO: Thomson Reuters (Healthcare) Inc. Updated 2011.
12. Vancocin. Manufacturer package insert. Updated 2004. FDA Web Site. Last accessed: 12/05/2011 Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/50606slr020_vancocin_lbl.pdf
13. Vancocin . In: DrugDex[Micromedex Online]. Greenwood Village, CO: Thomson Reuters (Healthcare) Inc. Updated 2011

Appendix 1:

Table 1. Pharmacokinetic comparison of fidaxomicin, metronidazole and vancomycin.

Parameters	Fidaxomicin[1]	Metronidazole[11]	Vancocin*[12,13]
Route of administration	Oral (PO)	Oral (PO)	Oral (PO)
Oral bioavailability	Minimal absorption from GI tract	80%	Poorly absorbed
Cmax (ng/mL)	5.20 + 2.81		
Protein Binding	N/A	< 20%	~ 50%-55%
Half-life (h)	11.7 for drug, 11.2 for active metabolite	~ 8 (range 6-12) Longer in neonates, hepatic and renal impairment.	4-6
Metabolism	Hydrolysis in intestine, has active metabolite	Hepatic (30%-60%)	No apparent metabolism
Elimination	Feces (> 92% unchanged drug, and metabolites).	Renal (60%-80% as unchanged drug), feces (6%-15%).	PO (feces)
Renal Impairment Dose Adjustment	Not recommended	GFR <10mL/min, reduce normal dose by 50% at usual interval.	Recommended
Hepatic Impairment Dose Adjustment	Not evaluated	Recommended for severe impairment	N/A
Food effect on pharmacokinetics	Not clinically significant. May take drug regardless to meals.	Lowers and delays peak concentration. No effect on total drug absorbed.	

*****The parenteral form of Sterile Vancomycin Hydrochloride may be administered orally for treatment of antibiotic-associated psuedomembraneous colitis produced by *C. difficile*. The appropriate dose may be diluted in 1 oz of water and given to the patient to drink. Common flavoring syrups may be added to the solution to improve the taste for oral administration. The diluted solution may be administered via a nasogastric tube.

Appendix 2: Suggested PA Criteria

Fidaxomicin (Dificid)

Goal(s):

- To optimize appropriate treatment of *Clostridium difficile* associated diarrhea

Length of Authorization: 10 days

Preferred Alternatives: Listed at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml
Requires PA: fidaxomicin (Dificid®).

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the patient have a diagnosis of *Clostridium Difficile* Associated Diarrhea (CDAD)? (ICD-9 008.45)?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Will the prescriber consider a change to a preferred antibiotic? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee.	**Yes:** Inform Provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml	**No:** Go to #4
4. Does the patient have a documented trial of appropriate therapy with vancomycin or metronidazole for a first recurrence or contraindication to therapy?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny (medical appropriateness)
5. Does the patient have severe, complicated CDAD (life-threatening or fulminant infection or toxic megacolon)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Approve for up to 10 days

P&T Board Action: 4-25-2012
Revision(s):
Initiated:

Appendix 3: Quality Assessment and evidence grading methods:

The methodology and tools described below is the standard approach that will be used by OSU staff to review drugs for the Oregon Health Authority Pharmacy and Therapeutics (P&T) Committee. These methods and tools were developed by the Oregon Evidence-based Practice Center Drug Effectiveness Review Project (DERP) and used in their systematic review process. The full Review Methods for the DERP can be found on their website at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm. These methods will evolve to best fit the needs of the P&T Committee and to stay current with the standards of evidence review and principles of best evidence.

Quality Assessment

Trials included in reviews for drugs will be assessed for internal validity using the quality assessment tool below. Each trial will subsequently be rated as Good, Fair, or Poor. Studies rated as good meet all the criteria and studies that have a fatal flaw are rated poor quality. The remainder will be rated in the Fair category.

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?	
• Yes	Use of the term "randomized" alone is not sufficient for a judgment of "Yes". Explicit description of method for sequence generation must be provided. Adequate approaches include: Computer-generated random numbers, random numbers tables
• No	Randomization was either not attempted or was based on an inferior approach (e.g., alternation, case record number, birth date, or day of week)
• Unclear	Insufficient detail provided to make a judgment of yes or no.
2. Was the treatment allocation concealed?	
• Yes	Adequate approaches to concealment of randomization: Centralized or pharmacy-controlled randomization, serially-numbered identical containers, on-site computer based system with a randomization sequence that is not readable until allocation *Note: If a trial did not use adequate allocation concealment methods, the highest rating it can receive is "Fair".*
• No	Inferior approaches to concealment of randomization: Use of alternation, case record number, birth date, or day of week, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
• Unclear	No details about allocation methods. A statement that "allocation was concealed" is not sufficient; details must be provided.
3. Were groups similar at baseline in terms of prognostic factors?	
• Yes	Parallel design: No clinically important differences Crossover design: Comparison of baseline characteristics must be made based on order of randomization. *Note: Determine beforehand which prognostic factors are important to consider. A statistically significant difference does not automatically constitute a clinically important difference.*
• No	Clinically important differences
• Unclear	Statement of "no differences at baseline", but data not reported; or data not reported by group, or no mention at all of baseline characteristics. For crossover design, only reported baseline characteristics of the overall group.
4. Were eligibility criteria specified?	
• Yes	Eligibility criteria were specified a priori.
• No	Criteria not reported or description of enrolled patients only.
5. Were outcome assessors blinded to treatment allocation? **6. Was the care provider blinded?** **7. Was the patient blinded?**	
• Yes	Explicit statement(s) that outcome assessors/care provider/patient were blinded. Double-dummy studies and use of identically-appearing treatments are also considered

	sufficient blinding methods for patients and care providers.
• No	No blinding used, open-label
• Unclear, described as double-blind	Study described as double-blind but no details provided.
• Not reported	No information about blinding
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?	
• Yes	All patients that were randomized were included in the analysis. Specify if imputation methods (e.g., last-observation carried forward) were used. OR Exclusion of 5% of patients or less is acceptable, given that the reasons for exclusion are not related to outcome (e.g., did not take study medication) and that the exclusions would not be expected to have an important impact on the effect size
• No	Exclusion of greater than 5% of patients from analysis OR less than 5%, with reasons that may affect the outcome (e.g., adverse events, lack of efficacy) or reasons that may be due to bias (e.g., investigator decision)
• Unclear	Numbers analyzed are not reported
9. Did the study maintain comparable groups?	
• Yes	No attrition. OR, the groups analyzed remained similar in terms of their baseline prognostic factors.
• No	Groups analyzed had clinically important differences in important baseline prognostic factors
• Unclear	There was attrition, but insufficient information to determine if groups analyzed had clinically important differences in important baseline prognostic factors
10. Were levels of crossovers (≤ 5%), nonadherence (≤ 20%), and contamination (≤ 5%) acceptable?	
• Yes	Levels of crossovers, adherence and contamination were below specified cut-offs.
• No	Levels or crossovers, adherence, and contamination were above specified cut-offs.
• Unclear	Insufficient information provided to determine the level of crossovers, adherence and contamination.
11. Was the rate of overall attrition and the difference between groups in attrition within acceptable levels?	
Overall attrition: There is no empirical evidence to support establishment of a specific level of attrition that is universally considered "important". The level of attrition considered important will vary by review and should be determined a priori by the review teams. Attrition refers to discontinuation for ANY reason, including lost to follow-up, lack of efficacy, adverse events, investigator decision, protocol violation, consent withdrawal, etc.	
• Yes	The overall attrition rate was below the level that was established by the review team.
• No	The overall attrition rate was above the level that was established by the review team.
• Unclear	Insufficient information provided to determine the level of attrition
Differential attrition	
• Yes	The absolute difference between groups in rate of attrition was below 10%.
• No	The difference between groups in the overall attrition rate or in the rate of attrition for a specific reason (e.g., adverse events, protocol violations, etc.) was 10% or more.
• Unclear	Insufficient information provided to determine the level of attrition

Grading the strength of the evidence:
The evidence will be graded as high, moderate, low or insufficient and use an approach also accepted by the Evidence-based Practice Center Program. A comprehensive evaluation will assess the major domains including are risk of bias, consistency, directness, and precision of the evidence. After assessing each of the domains for the group of studies, an overall assessment is made for each measured outcome being assessed for benefit and harm. When there is no evidence available or the evidence is too limited or too indirect to make conclusions, the evidence will be described as insufficient. The following table provides the definitions adopted by the Evidence-based Practice Center for these terms.

Strength of Evidence Grades and Definitions[1]:

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit the estimation of an effect.

References:
Oregon Evidence-Based Practice Center. Drug Effectiveness Review Project: Systematic Review Methods and Procedures. Available at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/upload/DERP_METHODS_WEB_Final_January-2011-2.pdf