Brand Name: Dificid

Generic Name: fidaxomicin

Manufacturer [1,2,3,4,5]**:** Optimer Pharmaceuticals, Inc.

Drug Class[1,2,3,4,5]: Macrolide Antibiotic

Uses [1,2,3,4,5]**:**

Labeled Uses: Treatment of *Clostiridum Difficile*- associated diarrhea (CDAD)

Unlabeled Uses: None

Mechanism of Action [1,2,3,4,5]**:**

Inhibits the polymerase sigma subunit resulting in inhibition of protein (RNA) synthesis by RNA polymerases and cell death in susceptible organisms including *C.difficile;* bactericidal.

Pharmacokinetics[1,2,3,4,5]:

Absorption:

T_{max} (oral)	2 hours
$t_{1/2}$	11.7 hours
Bioavailability	Not reported; fidaxomicin remains mainly in the gastrointestinal tract after oral absorption
V_d	Not reported; fidaxomicin remains mainly in the gastrointestinal tract after oral absorption
Protein binding	Not reported; fidaxomicin remains mainly in the gastrointestinal tract after oral absorption

Metabolism: Primary route is hydrolysis in the intestinal tract at the isobutyryl ester to form its main and active metabolite, OP-1118, this metabolism is not dependent on cytochrome P450 enzymes.

Elimination: Feces (>92% unchanged drug and metabolites); urine (<1% as metabolite)

Safety and Efficacy:

Louie T, Miller M, Donskey C, Mullane K, Goldstein EJ: Clinical outcomes, safety, and pharmacokinetics of OPT-80 in a phase 2 trial with patients with Clostridium difficile infection. Antimicrob Agents Chemother. 2009 Jan; 53(1):223-8.

Study Design: dose-finding, randomized, open-label phase II study to select a safe and effective dose of OPT-80 for treatment of mild to moderately severe C. difficile infection(CDI).

Description of Study: *Methods:* Eligible patients were males and females at least 18 years old with ≥3 unformed stools/day or ≥6 unformed stools in a 36-h period, who had a positive C. difficile toxin results by enzyme immunoassay or cell cytotoxicity assay, and received treatment with another antimicrobial agent (metronidazole or vancomycin) for < 24 h. Patients with a primary episode or 1st relapse of disease were eligible. Patients with severe disease, needing antibiotic therapy or having Crohn's disease or ulcerative colitis were excluded. 48 evaluable subjects were randomized to receive 50, 100, or 200 mg of OPT-80 orally every 12 hours for 10 days as treatment for mild to moderately severe CDI and monitored for 6 weeks after completion. Efficacy analysis was performed with the modified intent-to-treat population.
Outcome Results: Plasma concentrations were below the lower limit of quantitation in almost one-half of patients and typically ≤20 ng/ml (5 to 1,000 ng/mL for both OPT-80 and OP-1118) across the dose range. The fecal concentration range of the assay for OPT-80 was 10 - 2,000 ng/ml, and for OP-1118 was 50 - 10,000 µg/ml. The mean of these fecal concentrations exceeded the MIC at which 90% of the isolates tested are inhibited by 2,000- to 10,000-fold with increasing dosages. OPT-80 was well tolerated and no side effects appeared to be due to study medications. Resolution of diarrhea or disease within 10 days was achieved in 71% (10/14) of the 100-mg/day group, 80% (12/15) of the 200-mg/day group, and 94% (15/16) of the 400-mg/day group. With increasing dosages, the median time to resolution of diarrhea was reduced from 5.5 to 3.0 days. Clinical cure rate (resolution of diarrheal disease without further treatment need) was 91%. At ~1 month after treatment, recurrence of CDI was seen in two patients, one in each of the 100-mg and 400-mg groups. Total relief was achieved by 37.5% of the 100-mg/day recipients, 50.0% of the 200-mg/day recipients, and 86.7% of the 400-mg/day recipients. The difference between the 100- and 400-mg/day treatment groups approached statistical significance (P = 0.0506 by Kaplan-Meier analysis and P = 0.0503 by Kruskal-Wallis test).

Limitations: Authors were affiliated with the manufacturer of Dificid. The main limitation to this study would be the lack of strong support for the efficacy of OPT-80, which is proven by later phase III trials.

Conclusion: The high clinical response, worthy tolerance, low recurrence rate, and more-complete and rapid symptom control with the highest dosage all support the selection of the 200-mg twice-daily dose (400 mg/day) for further clinical trials of OPT-80 for treatment of CDI.

Louie TJ, Miller MA, Mullane KM, et al: Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011; 364(5):422-431.

Study Design: prospective, multicenter, double-blind, randomized, parallel-group trial

Description of Study: *Methods:* 629 patients aged 16 years of age or older with confirmed C difficile infection were randomly assigned to a 10 day course of either oral vancomycin 125 mg four times daily (n=327) or oral fidaxomicin 200 mg twice daily with intervening placebo for the other two doses (n=302). Primary end point was clinical cure, resolution of symptoms and no need for further therapy after the end of the course of treatment in the modified intention to treat group and the per-protocol group. Secondary end point was recurrence of C. difficile infection and global cure, cure without recurrence.
Outcome Results: For clinical cure rates in the per protocol analysis, 92.1% (n=244/265) in the fidaxomicin group and 89.8% (n=254/283) in the vancomycin group (lower limit of 97.5% CI for difference, -2.6%). For clinical cure rates in the modified intention-to-treat analysis 88.2% (n=253/287) in the fidaxomicin group and 85.8% (n=265/309) in the vancomycin group (lower limit of 97.5% CI for difference, -3.1%). For secondary endpoints, there was a significantly lower rate of recurrence 4 weeks following therapy with fidaxomicin compared with vancomycin in both the modified intent to treat analysis (15.4% vs. 25.3%, P=0.005) and the per-protocol analysis (13.3% vs. 24.0%, P=0.004). Lower rates of recurrence were associated with non-North American Pulsed Field type 1 strains. Adverse event profiles were similar between treatment groups.

Limitations: All authors were affiliated with the manufacturer of Dificid.

Conclusions: Clinical cure rates after treatment with fidaxomicin were non-inferior to rates after treatment with vancomycin. As for recurrence of C. difficile infection, fidaxomicin was associated with a significantly lower rate of recurrence associated with non-North American Pulsed Field type 1 strains.

Gorbach, S. PAR-101/OPT-90 versus vancomycin for the treatment of clostridium difficile associated diarrhea (CDAD)

Study Design: randomized, double blind, parallel study

Description of Study: *Methods:* 535 patients were enrolled from Apr 2007 to Dec 2009. Enrolled patients had to be 16 years or older, have a diagnosis of CDAD, and signed informed consent. Patients were excluded were those with life-threatening CDAD, toxic megacolon, pregnant, concurrent use of diarrheal agents, or participation in other trials. Patients were randomized to receive 125 mg of vancomycin 4 times daily (n=260) or PAR-101/OPT-80 200 mg twice daily (n=264). Primary outcome measure was to investigate the cure rate at the end of therapy with of PAR-101/OPT-80 vs. vancomycin in patients with CDAD. Secondary outcome measures include recurrences (re-treatment) and global cure rate (a cure response at the end of treatment and no recurrence at any time up to post study visit). *Outcome Results:* a modified intent to treat population (mITT) included eligible patients who received at least one dose of study medication. The cure rate at the end of therapy for vancomycin was 86.7/256 (95% CI 82.0 to 90.4) and for PAR-101/OPT-80 was 87/7253 (CI 95%, 83.1 to 91.2); which concluded that treatments were non-inferior to each other (95% CI, -4.8 to 6.8). For secondary analysis of recurrence using the Chi-squared method, 27% of patients on vancomycin and 12.6% of patients on PAT-101/OPT-80

received re-treatment (95% CI, -21.6 to -7.0; P=0.001). Global cure rate was 63.3% in the vancomycin group and 76.7% in the PAR-101/OPT-80 group (95% CI, 5.4 to 21.1, P =0.001).

Limitations: the author of the clinical trial, Sherwood Gorach, MD, is an investigator for the manufacturer of Dificid. The clinical trial was also not published or peer reviewed.

Conclusions: Clinical cure rates of PAR-101/OPT-80 were not inferior to vancomycin. As for recurrence and global cure rates, PAR-101/OPT-80 had significantly greater rates compared to vancomycin.

Contraindications [1,2,3,4,5]:

None have been determined

Precautions [1,2,3,4,5]**:**

Lack of confirmed or strongly suspected Clostridium difficile-associated diarrhea (CDAD); increased risk of bacterial drug resistance

Pregnancy: U.S. FDA Pregnancy Category B

Breastfeeding: Thomson Lactation Rating: infant risk cannot be ruled out. Available evidence and expert consensus is inconclusive for determining infant risk and it is unknown whether fidaxomicin is excreted in human milk; therefore, caution is advised. Weigh the potential benefits of treatment against risks before prescribing this drug during breastfeeding.

Adverse Events[3,4] **:**

> 10%:

Gastrointestinal

Nausea (11%)

2% to 10%:

Gastrointestinal

Gastrointestinal hemorrhage (4%)
Abdominal pain (6%)
Vomiting (7%)

Hematologic

Anemia (2%)
Neutropenia (2%)

< 2%:

Dermatologic

Pruritis
Rash

Gastrointestinal

Abdominal distension
Abdominal tenderness
Bowel obstruction
Flatulence
Indigestion
Megacolon

Dyspepsia

Hematologic

Platelet count below reference range

Miscellaneous

Hyperglycemia
Metabolic acidosis
Serum bicarbonate level abnormal
Alkaline phosphatase raised
Increased liver enzymes

Drug Interactions[1,3,4]:

There are no known significant interactions

Dosing Administration[1,3,4]:

Adult Dosage

For Clostridium difficile associated diarrhea: the recommended dose is 200 mg orally twice daily with or without food for 10 days

Pediatric Dosage

Safety and efficacy have not been studied in patients < 18 years of age

Dosage in Hepatic Impairment

No dosage adjustment needed (minimally absorbed)

Dosage in Renal Failure

No dose adjustment needed

Dosage in Geriatric Patients

No dose adjustment needed

Dosage according to gender

No dose adjustment needed

Conclusion:

Fidaxomicin, a macrolide antibiotic, is an effective treatment for *Clostridium Difficile* associated diarrhea (CDAD) in adults > 18 years of age. Fidaxomicin is safe to use, with minimal side effects and no known drug interactions. Phase III trials have proven Dificid to be associated with lower recurrence rates after treatment of CDAD than vancomycin, which is an important factor for eradication of the infection. Though Dificid is an equally, if not an overall more, effective treatment for CDAD, questions arise such as will resistance develop and will patients and insurance companies be willing to pay the extra cost for Dificid? Cost is a significant consideration when choosing Dificid as a treatment as opposed to vancomycin for CDAD. Though, if patients fail other therapy, this may be the only option despite the cost. Future studies and clinical use of fidaxomicin will show how beneficial its role will be as treatment for CDAD.

Recommended References:

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8. Louie TJ, Miller MA, Mullane KM, et al: Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011; 364(5):422-431.
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Michelle Gianni, Doctor of Pharmacy Candidate