PDL NEW DRUG REVIEW

Proprietary Name: Dificid®
Common Name: fidaxomicin
PDL Category: Macrolides/Erythromycins/Ketolides

Comparable Products	Preferred Drug List Status
Metronidazole	Preferred
Vancomycin	Preferred

Summary

Indications and Usage: Treatment of *Clostridium difficile*-associated diarrhea (CDAD). To reduce the development of drug-resistant bacteria, and to maintain the effectiveness of Dificid®, it should only be used to treat proven or strongly suspected infections caused by *Clostridium difficile*. This is a pregnancy category B medication. The safety and efficacy of use in children under the age of 18 have not been established.

Drug Interactions: Fidaxomicin is a substrate of P-glycoprotein (P-gp). Cyclosporine is an inhibitor of P-gp, and when co-administered with fidaxomicin, plasma levels of fidaxomicin were significantly increased. However, fidaxomicin may be used concomitantly with P-gp inhibitors with no dose adjustment recommended.

Dosage Forms: Tablets: 200mg

Recommended Dosage: Take one tablet twice daily for 10 days, with or without food. Dosage adjustment is not required with renal impairment. The effect of use in those with hepatic impairment has not been evaluated; however, as Dificid® does not undergo significant hepatic metabolism, it is thought that use in those with hepatic impairment would not be significantly affected.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for vancomycin.* The most common adverse events reported with Dificid® includes anemia (0%), neutropenia (1%), nausea (0%), vomiting (1%), abdominal pain (2%), and gastrointestinal hemorrhage (2%).

Contraindications: There are currently no contraindications listed in the prescribing information.

Manufacturer: Optimer Pharmaceuticals, Inc

Analysis: Fidaxomicin, the active ingredient of Dificid®, is a macrolide antibiotic that works locally in the gastrointestinal tract to eradicate *C. difficile*. As there is minimal systemic absorption, Dificid® is not effective or approved for use as treatment of systemic infections.

In a study by Louie et al[2] (N=629), fidaxomicin was compared with vancomycin treatment in adults with *C. difficile* to assess for the clinical cure and recurrence rates of *C. difficile* infection. Fidaxomicin was shown to be non-inferior to vancomycin, with a clinical cure of 88.2% with fidaxomicin vs 85.8% with vancomycin (NNT=42); however, a significantly lower rate of recurrence was seen with fidaxomicin vs vancomycin (15.4% vs 25.3%, p=0.005; NNT=11).

A study by Cornely et al[3] (N=535) also compared the safety and efficacy of fidaxomicin with vancomycin in adult subjects with *C. difficile*. The non-inferiority of fidaxomicin vs vancomycin was assessed, as measured by the clinical cure and sustained clinical response rates. Results suggest that 87.7% of the fidaxomicin group had clinical cure vs 86.8% of the vancomycin (p=0.754), thus non-inferiority was proven. , Statistically more patients in the vancomycin group had recurrence of infection vs fidaxomicin (26.9% vs 12.7%, p=0.002; NNT=8). Thus, the fidaxomicin group had a significantly higher sustained clinical response vs the vancomycin group (76.6% vs 63.4%, p=0.001; NNT=8). Of special interest, this reduction in recurrences was not noted in those patients infected with the hypervirulent NAP1/B1/027 strain.

A 2011 systematic review by Drekonja et al[4] included 11 randomized trials (N=1463) to assess the effectiveness of antibiotics for the treatment of *C. difficile*. Of the included studies, there were 9 found for vancomycin, followed by 5 for metronidazole, 2 each for bacitracin and nitazoxanide, and only study each included for fidaxomicin and rifampin. The authors concluded that fidaxomicin, metronidazole, and vancomycin were all effective treatments for the initial cure of *C. difficile*. Nevertheless, while one agent was not found to be superior to another, fidaxomicin was found to have fewer recurrences as compared with vancomycin.

There is no evidence at this time to support that Dificid® is more efficacious or safer than the currently available, more cost effective medications. Therefore, it is recommended that Dificid® remain non-preferred and be available to those who have relapses with, fail on or are unable to tolerate any preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Dificid [package insert]. San Diego, CA: Optimer Pharmaceuticals, Inc; 2011.

[2] Louie TJ, Miller MA, Mullane KM,e t al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N*EJM*. 2011; 264(5): 422-31.

[3] Cornely OA, Crook DW, Esposito R, 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*. 2012. 12(4): 281-9.

[4] Drekonja DM, Butler M, MacDonald R, et al. Comparative effectiveness of *Clostridium difficile* treatments: a systematic review. *Ann Intern Med.* 2011; 155(12): 839-47.