

CA-ADAP Drug Review: Fidaxomicin (DIFICID) for *Clostridioides difficile*

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CA-ADAP Drug Review: AGENDA

1 Drug Background and Information

2 Disease Background

3 Clinical Trials

4 Discussion

Fidaxomicin (DIFICID)



- **Indication:** For treatment of *C. difficile*-associated diarrhea in adult and pediatric patients 6 months+
- **Dosage and Administration:**
 - Adults: One (1) 200mg tablet by mouth twice daily x10days
 - Pediatrics (6 mos - <18yrs):
 - Tablets – weight at least 12.5kg: One (1) 200mg tablet by mouth twice daily x10days
 - Oral Suspension – weight at least 4kg: Weight-based dosing of oral suspension (included in package insert)

Fidaxomicin Safety Information



- Acute hypersensitivity reactions have been reported
- The most common adverse reactions in adults:
 - Nausea (11%)
 - Vomiting (7%)
 - Abdominal pain (6%)
 - GI Hemorrhage (4%)
 - Anemia (2%)
 - Neutropenia (2%)
- The most common adverse reactions in pediatric patients:
 - Pyrexia (13.3%)
 - Abdominal pain (8.2%)
 - Vomiting (7.1%)
 - Diarrhea (7.1%)
 - Constipation (5.1%)
 - Increased aminotransferases/rash (5.1%)

Bacterial Enteric Infections & PLWH



- Rates of Gram-negative infections are at least 10x higher
 - Rates decline when treated with ART
- *C. diff*-associated infection (CDI) is common
 - Low CD4 count (<50 cells/mm³) is a disease risk factor
- Incidence of community-onset CDI is increasing
 - Health care providers should consider CDI when evaluating outpatient diarrheal illnesses
- The likely source for infections is contaminated food/water
 - Sexual activity with fecal-oral exposure increases risk
 - HIV-associated alterations in mucosal immunity or intestinal integrity, + treatment with acid-suppressants may increase risk
- Severe infection often is defined as six (6) or more loose stools/day
 - The risk of more serious illness increases with immunosuppression

C. Difficile diarrhea



- Patients at risk for *C. diff* diarrhea include:
 - Received/currently receiving antibiotics (including prophylaxis)
 - Hospitalization in past 4-6 weeks
 - Reside in LTC
 - CD4 < 200 cells/mm³
 - Taking acid-suppressive meds
- Only those with diarrhea (3+ loose stool/24hr) should be tested for *C. diff*
- Only stool samples that take the shape of the container should be tested for *C. diff* toxin B.

CDI Treatment



- Initial Episode:
 - Fidaxomicin increased the likelihood of sustained clinical response compared to oral vancomycin (RR 1.16; 95% CI, 1.09-1.24)
 - Fidaxomicin was equivalent to oral vancomycin in initial clinical cure, serious adverse events, and all-cause mortality
 - **The 2021 IDSA CDI guidelines update for adults suggests treatment with fidaxomicin, rather than oral vancomycin, for initial CDI, whether CDI is severe or nonsevere**
 - Fidaxomicin should be considered in PLWH and CDI
 - Oral vancomycin is still also acceptable
 - Metronidazole is considered an alternative to fidaxomicin and vancomycin

Clinical Trials



Efficacy and safety of fidaxomicin for the treatment of *Clostridioides difficile* infection



- **Objective:** To demonstrate non-inferior efficacy of fidaxomicin vs vancomycin
- Phase III, vancomycin-controlled, double-blind, parallel group study
 - 212 patients randomly assigned fidaxomicin 200mg BID or vancomycin 125mg QID x 10 days
 - Primary endpoint was global cure rate of CDI
- Results:
 - Non-inferiority margin set at 10%
 - Fidaxomicin: 70/104 (67.3%) cured
 - Vancomycin: 71/108 (65.7%) cured
 - Non-inferiority was **not** demonstrated
 - Post-hoc analysis of patients who received at least 3 days' treatment
 - Fidaxomicin: 70/97 (72.2%) cured
 - Vancomycin: 71/106 (67.0%) cured
 - Recurrence rate was lower in fidaxomicin (19.5%) than vancomycin (25.3%)

Extended-pulsed fidaxomicin vs vancomycin for *Clostridioides difficile* infection in patients 60 years and older (EXTEND)



- **Objective:** To compare clinical outcomes of extended-pulsed fidaxomicin with standard vancomycin
- Randomized, controlled, open-label, superiority study
 - 364 hospitalized adults aged 60+ with confirmed *C.diff* infection
 - Patients assigned fidaxomicin 200mg BID on days 1-5, then Qday on alternate days 7-25 or vancomycin 125mg QID on days 1-10
- **Results:**
 - Fidaxomicin: 124/177 (70%) cured
 - Vancomycin: 106/179 (59%) cured
 - Incidence of adverse events did not differ between the groups
 - Extended-pulsed fidaxomicin was superior to standard-dose vancomycin
 - Recurrence rates with fidaxomicin were the lowest observed thus far (from date of publishing) for *C.diff* infection

Fidaxomicin versus vancomycin for infection with *Clostridium difficile*



- **Objective:** To compare efficacy and safety of fidaxomicin with vancomycin
- Multicenter, double-blind, randomized, non-inferiority trial
 - 535 patients aged 16+ assigned fidaxomicin 200mg Q12h or vancomycin 125mg Q6h x10 days
 - Primary endpoint was clinical cure
- Results:
 - Non-inferiority margin set at 10%
 - Fidaxomicin: 198/216 (91.7%) cured
 - Vancomycin: 213/235 (90.6%) cured
 - Non-inferiority **was** demonstrated (one-sided 97.5% CI -4.3%)
 - Occurrence of ADRs did not differ between groups
 - 20/264 fidaxomicin and 17/260 vancomycin died

Fidaxomicin versus vancomycin for Clostridium difficile infection



- **Objective:** To compare efficacy and safety of fidaxomicin with vancomycin
- Phase III, randomized, double-blind, parallel group study
 - 629 patients assigned fidaxomicin 200mg BID or vancomycin 125mg QID x10 days
 - Primary endpoint was clinical cure
 - Secondary endpoints were recurrence of C.diff infection within 4 weeks after treatment and global cure (no recurrence)
- Results:
 - Non-inferiority margin set at 10%
 - Fidaxomicin: 92.1% cured
 - Vancomycin: 89.8% cured
 - Non-inferiority was **not** demonstrated
 - Significantly fewer patients in fidaxomicin group had recurrence
 - ADRs similar for both

Treating *Clostridioides difficile*-associated infection (CDI)



Preferred Therapy (Severe or Nonsevere CDI*)

- Fidaxomicin 200mg (PO) 2 times per day for 10 days
- Vancomycin 125mg (PO) 4 times per day for 10 days

Alternative Therapy for Nonsevere CDI*

- If fidaxomicin or vancomycin access is limited and if CDI is nonsevere, outpatient disease: metronidazole 500mg PO 3 times per day for 10 days

Note: Based on clinical trials, vancomycin is superior to metronidazole for therapy of CDI

Formulary Management Recommendations: *C.diff* Treatment



Fidaxomicin (DIFICID)

Recommend addition to the ADAP
formulary.

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