Fidaxomicin (DIFICID™)
National Drug Monograph Addendum
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Background

Disease state, prevalence, VA specific data if available

- *Clostridioides difficile* infection (CDI) is a significant cause of antibiotic-associated diarrhea/colitis.[6,7]
- Recurrence occurs in up to 30% of initial episodes, and risk increases with each subsequent episode.[6]
- Risk factors for recurrent CDI include age >65 years, concomitant antibiotic use during CDI treatment, immunosuppression, and inflammatory bowel disease.[5,18]
- In the VA, approximately 10,000-12,000 cases occur each year, with healthcare-facility-associated CDI decreasing from 95 to 88 cases per 100,000 persons and community-associated CDI increasing from 78 to 100 cases per 100,000 persons from 2009 to 2013.[33] Other VHA surveillance studies have suggested increases in community-associated CDI.[16,34] A study of epidemiology of CDI in VHA from 2003-2014 found that recurrent CDI occurred in 17% of cases, and of those 34% had at least one additional recurrence.[21] Other risk factors for recurrence identified in VA studies include use of proton-pump inhibitors, immunosuppressants, and non-severe and community onset CDI episodes.[22,23]

Rationale for the addendum (e.g. new data, new guidelines):

- Since the initial review of Fidaxomicin by the VANF in February 2012, two additional randomized controlled trials have informed recent guideline updates for the treatment of CDI, both of which broaden the role of fidaxomicin as a treatment option for CDI.[3,4] VHA Criteria For Use (CFU) were established in 2012, and updated in 2017 for use in patients with two or more CDI episodes treated with PO vancomycin, including one tapered or pulse course. A recent study evaluating fidaxomicin use in the VA found[17]:
    - Use of fidaxomicin increased steadily from 2011 through 2015
    - Only 9.1% of treatment courses were consistent with the fidaxomicin CFU, with most given for a first recurrence (25%) or initial episode (24%) of CDI and with 21% prescribed to patients without a positive test for *C.difficile.*
    - A secondary analysis found failure and recurrence rates of 6.8% and 24.4% respectively.
    - This study suggests both a need to update the CFU to be consistent with updated guidelines, as well as a role for local antimicrobial stewardship programs to improve diagnostic and antimicrobial stewardship in patients with CDI, as molecular testing is highly sensitive, can detect asymptomatic CDI colonization, and is associated with increased CDI incidence in hospitalized Veterans.[15]
- Both the Infectious Diseases Society of America/Society of Healthcare Epidemiologists (IDSA/SHEA) and the American College of Gastroenterology (ACG) updated CDI guidelines in 2021. **Both guidelines place fidaxomicin and vancomycin as first-line options for initial and recurrent CDI, although the IDSA guidelines suggest fidaxomicin may be preferred, particularly in patients at high risk of recurrence**[5,7]
- Table 1 outlines recommendations for initial and recurrent CDI from both sets of guidelines. Table 2 provides efficacy results from the four available, industry-funded, randomized controlled trials. Additional efficacy includes information from real world studies evaluating use of fidaxomicin in VHA.

Table 1: Summary of 2021 CDI Guideline Recommendations[5-8]

CDI classification	IDSA/SHEA Guidelines (2017/2021)	ACG Guidelines (2021)
Initial episode, non-severe **Definition: WBC count ≤15,000 cells/ml AND SCr <1.5 mg/dl (IDSA/SHEA)**	**Suggest** Fidaxomicin (FDX) 200mg by mouth BID for 10 days over vancomycin (VAN) 125mg QID for 10 days but **VAN is an acceptable alternative** *(conditional rec., moderate certainty of evidence)* Initial therapy recs. do not differ by severity, but state FDX may be most beneficial in those at greater risk of recurrence	VAN standard regimen *(Strong rec., low quality of evidence)* OR FDX standard regimen *(Strong rec., moderate quality of evidence)* OR Metronidazole (MTZ) 500mg by mouth TID for 10 days for low-risk patients *(Strong rec., moderate quality of evidence)*
Initial episode, severe **Definition: WBC count >15,000 cells/ml AND SCr ≥1.5 mg/dl (IDSA/SHEA)**	Same as above – 2021 guidelines do not differentiate by severity, other than considering severe CDI a risk factor for recurrence	VAN standard regimen *(Strong rec., low quality of evidence)* OR FDX standard regimen *(Conditional rec., very low quality evidence)*
First recurrence **Definition: episode of symptom onset and positive assay result following initial episode in the previous 2-8 weeks (IDSA/SHEA)**	**PREFERRED:** FDX standard regimen **OR** 200mg BID for 5 days followed QOD for 20 days (extended-pulsed regimen) **ALTERNATIVE:** VAN tapered and pulsed regimen (i.e. 125mg QID x 10-14 days, BID x 7 days, QD x 7 days, and then every 2-3 days for 2-8 weeks) **OR** VAN 125mg QID x 10 days if metronidazole used for initial episode *(Conditional rec., low quality of evidence)*	VAN in a tapered and pulsed regimen after an initial course of FDX, VAN, or MTZ *(Strong recommendation, very low quality of evidence)* FDX after an initial course of VAN or MTZ *(Conditional recommendation, moderate quality of evidence)*
Second or subsequent recurrence **Definition: episode of symptom onset and positive assay result following previous episode in the previous 2-8 weeks**	FDX standard **OR** extended-pulse regimen VAN in a tapered and pulsed regimen (as above) VAN 125mg by mouth QID for 10 days followed by rifaximin 400mg TID for 20 days Fecal microbiota transplant (FMT) after treatment for 2 prior recurrences *(Conditional rec., low quality of evidence)*	The ACG guidelines do not specifically recommend FDX for subsequent recurrences, instead recommend FMT for second or further recurrences *(Strong recommendation, moderate quality of evidence)*
Fulminant CDI **Definition: hypotension or shock, ileus, megacolon (IDSA/SHEA)**	VAN 500mg PO/NGT QID [for first 48-72 hours per ACG] +/- MTZ 500mg IV q8h (particularly if ileus present); if complete ileus, consider VAN retention enema (500mg/100 ml NS) PR q6h **FDX not recommended in fulminant CDI**	

Relevant Efficacy Data

Table 2: Efficacy of Fidaxomicin

Trial	Study Design	Demographics	Outcomes	Comments
Randomized Controlled Trials				
Louie et al (2011)[1] Prospective, multi-center, randomized, double-blind, parallel-group non-inferiority trial in USA and Canada	**Inclusion:** ≥16 y/o patients diagnosed with CDI randomized 1:1 to FDX standard regimen (200mg BID x 10 d) OR VAN standard regimen (125mg QID x 10 d) **Exclusion**: fulminant CDI, previous FDX exposure, more than one prior CDI episodes within 3 mo. **Primary outcome**: Clinical cure (2 days after end of therapy [EOT])	**mITT population**: FDX n=287 VAN n=309 **Demographics [FDX, VAN]:** Female: 57%, 55% Mean age: 60, 63 Severe CDI: 39%, 40% Initial CDI: 83%, 83% Inpatient: 58%, 61% CDI antibiotics in previous 24h: 38%, 40%	**Primary:** Clinical cure (2 days after EOT) [FDX, VAN]: 88%, 86%; p>0.05 **Secondary:** **Recurrence (at 28 days) [FDX, VAN]:** 15%, 25%; p=0.005 **Global cure (at 28 days)** [FDX, VAN]: 75%, 64%; p=0.006	FDX met criteria for non-inferiority to VAN for clinical cure of CDI Significantly lower recurrence and higher global cure rates than VAN
Cornely et al (2012)[2] Prospective, multi-center, randomized, double-blind, non-inferiority trial in Europe, USA, Canada	Same inclusion/exclusion and treatments as above **Primary outcome:** Sustained response (global cure): clinical cure without recurrence	**mITT population**: FDX n=252 VAN n=257 **Demographics [FDX,VAN]:** Female: 59%, 63% Mean age: 64, 63 Severe CDI: 25%, 24% Initial CDI: 84%, 86% Inpatient: 69%, 67% Concomitant antibiotics at any time: 33%, 27%	**Primary:** Clinical cure (2 days after EOT) [FDX, VAN]: 88%, 87%; p=0.754 **Secondary:** Recurrence (at 28 days) [FDX, VAN]: 13%, 27%; p=0.0002 Sustained response (at 28 days) [FDX, VAN]: 77%, 63%; p=0.001	Similar findings as Louie et al study Subgroup analysis of patients on concomitant antibiotics: reduced clinical cure rates for VAN but not FDX
Guery et al (2018)[3] Prospective, multi-center, randomized, open-label, RCT in Europe	**Inclusion:** hospitalized patients ≥60 y/o without IBD with CDI randomized 1:1 to extended-dose FDX (200mg bid x 5 d, then 1 tab QOD on days 7-25) OR standard dose VAN **Exclusion**: More than 2 CDI episodes within 3 months **Primary outcome**: Sustained clinical cure 30 days after EOT (day 55 for FDX, day 40 for VAN) in modified full analysis set (mFAS) population	**mFAS**: FDX n=177 VAN n=179 **Demographics [FDX, VAN]:** % female: 60%, 56% % white: 84%, 85% Median age: 75, 75 % Severe CDI: 36%, 37% % Initial CDI: 80%, 78% % non-CDI antibiotic use: 72%, 72% % presence of cancer: 21%, 21%	**Primary:** Sustained clinical cure 30 days after EOT [FDX, VAN]: 70%, 59%; p=0.03 **Secondary:** Sustained clinical cure [FDX, VAN]: Day 40: 75%, 59%; p=0.001 Day 55: 70%, 55%; p=0.004 Day 90: 66%, 51%; p=0.007 Clinical response 2 days after EOT [FDX, VAN]: 78%, 82%; p=0.399	Only known study evaluating extended-dose FDX (compared to standard dose VAN); total treatment course equivalent between extended-dose and standard dose FDX Longer time to resolution of diarrhea (hours) for FDX: 34 (25-49), 22 (10-30), p=0.068
Mikamo et al (2018)[4] Prospective, multi-center, randomized, double-blind, non-inferiority trial in Japan	**Inclusion:** hospitalized patients ≥20 y/o diagnosed with symptomatic CDI randomized 1:1 to FDX standard regimen OR VAN standard regimen **Exclusion**: fulminant CDI, concomitant CDI antibiotics, more than one prior CDI episodes within 3 months **Primary outcome**: global cure	**Population**: FDX: FAS n=104; mFAS n=87 VAN n=108; mFAS n=95 **Demographics [FDX, VAN]:** % female: 54%, 50% Mean age: 74, 75 % Severe CDI: 24%, 20% % Initial CDI: 87%, 85% % Antibiotic use for CDI prescreening: 95%, 97%	**Primary:** Global cure [FDX, VAN]: FAS: 67%, 66% **Secondary:** Clinical Cure [FDX, VAN]: FAS: 84%, 88% **Recurrence (mFAS)** [FDX, VAN]: 19.5%, 25.3% (treatment difference -4.9%, 95% CI -16.7 to 7.0)	Unlike prior RCTs, did not find a significant difference in outcomes between VAN and FDX, although numerically lower recurrences and higher global cure with FDX

Real world data in VHA

- Several studies have evaluated use of fidaxomicin across VHA
    - As noted above, a retrospective review of 1098 courses of FDX in VHA between 2011 and 2015 noted that only 9% were consistent with the VHA CFU, which did not change over time.[17] In addition, 13% were given in combination with VAN or MTZ and over 20% were given to patients without a positive test for CDI. The recurrence rate in 251 patients where outcomes were assessed was 24%. Exclusion from evaluation of clinical outcomes included ≤ 72 hours of FDX, use in combination with another CDI antibiotic, use in those without a positive test for CDI or having a positive test not within 72 hours of FDX initiation.
    - The same group of investigators completed a propensity matched retrospective cohort study of 213 Veterans treated with FDX vs. 639 treated with VAN for severe CDI (WBC ≥ 15K cells/mL or serum creatinine ≥ 1.5 times baseline).[24] Approximately 80% of courses were for recurrent disease. FDX was associated with significantly higher rates of initial failure with FDX (9.4%) vs. VAN (1.4%), primarily due to a change in therapy. Recurrence was identical at 24% in each group. No difference in mortality was found.
    - Finally, this group looked specifically at FDX vs. VAN in Veterans with recurrent CDI (1st or 2nd recurrence).[25] No difference in the composite endpoint of failure or recurrence was found in the 65 patients who received FDX (27.7%) or 195 patients who received VAN (21.5%). Recurrence was similar between the arms, but those treated with FDX had a higher rate of failure (6% vs. 1%, p=0.036). Of note, this study's population overlaps with the population evaluated in the study above on recurrent CDI
- These studies contrast with published RCTs, which suggest FDX is associated with lower rates of recurrence and higher rates of global cure. While some difference in the real-world VA studies may be due to unmeasured confounding with a non-randomized design, it also may suggest differences in efficacy of FDX in the VA population that were not apparent in the RCTs.
- One small real-world VHA study out of two VAMCs for hospitalized Veterans found early targeted use (within 5 days of positive CDI result) of FDX relative to VAN was associated with statistically lower rates of a composite of mortality and recurrence, including a 14% lower rate of recurrence seen with FDX. Unlike the VHA studies above, this study confirmed clinical criteria of CDI (3+ documented, unformed stools in preceding 24 hours or ileus with other causes of diarrhea being ruled out).[32] These results imply that optimizing diagnostic and antimicrobial stewardship for CDI can improve clinical outcomes of CDI in the Veteran population.

Efficacy Summary:

- Three of four randomized, blinded trials of FDX vs. VAN were associated with similar rates of clinical cure, higher rates of sustained/global cure, and rates of recurrence approximately 10% lower than VAN with FDX.
- In contrast, a 4th blinded RCT done in Japan did not find a difference between FDX and VAN with regards to recurrence or sustained/global cure. All four of the RCTs included patients with both mild-moderate and severe CDI, and in patients with either a first or second episode of CDI.
- A post-hoc subgroup analysis in RCT patients with first recurrence demonstrated increased sustained response 30 days post-treatment compared to vancomycin (RR: 1.27, 95% CI 1.05 to 1.54), however this effect was not seen at 90 days post-treatment (RR: 1.56, 95% CI 0.99 – 2.44)[6]
- Several real-world studies of FDX use in VHA failed to show a similar difference in failure or recurrence in specific populations of Veterans with CDI, including those with severe or recurrent infection. In fact, recurrence rates with FDX in this population were similar to those seen with VAN in the RCTs.[17,24,25] However, a lack of diagnostic and antimicrobial stewardship may have contributed to these results, as a smaller VHA study confirming the clinical criteria of CDI found results more consistent with RCT data for hospitalized Veterans.[32]
- Other non-VHA real world studies have also found results that were consistent with RCT findings.[30,31]

Safety

Updated relevant safety data:

- Pooled analysis of the above RCTs did not show a difference between fidaxomicin and vancomycin for drug-related adverse effects (RR: 1.02, 95% CI: 0.76 to 1.36) or mortality (RR: 0.9; 95% CI 0.66-1.73).[6]

Alternatives

Table 3: Alternatives for initial and recurrent *C. difficile* infection

Drug	Formulary status	Efficacy, guideline recommendations	Safety, pharmacokinetics, logistics, other considerations
Fidaxomicin (PO)[2,5-7,19]	F-PA	First-line for initial and recurrent non-fulminant CDI Generally equivalent to VAN for initial clinical cure, with increased global cure in 3 of 4 RCTs Minimal data for use with bezlotoxumab	PK: minimally absorbed, limited activity against normal gut flora Twice daily dosing Caution with macrolide allergy[14] High acquisition cost
Vancomycin (PO)[5-7,9]	Formulary	Lower sustained cure than FDX in 3 of 4 RCTs, but not in VA real-world data. Recommended as first-line alternative in initial CDI or as a tapered regimen in recurrent CDI Therapy of choice for fulminant CDI Long track record of use and familiarity	PK: minimal absorption Four times daily dosing and vancomycin taper for recurrent CDI is complicated and prolonged
Metronidazole (IV, PO)[6,7,10,20]	Formulary	Less effective than VAN in achieving clinical cure and sustained response one-month post-treatment Recommended only as an alternative agent in mild-to-moderate CDI if patient is low-risk or if first-line options unavailable or contraindicated For fulminant CDI, IV MTZ is recommended in combination with PO/PR VAN particularly if ileus is present A VA retrospective cohort study for suggested role in mild CDI in Veterans < 65 years[10]	PK: well absorbed; widely distributed to tissues including CSF; hepatically metabolized; excreted in urine (60-80%) and feces (6-15%) Adverse effects: nausea (12%), headache (18%), metallic taste (9%), bacterial infection (7%), genital pruritus (5%), CNS effects (risk factors include prolonged or repeated use), disulfiram-like reaction (contraindicated with use of disulfiram within the past two weeks, or concurrent or recent use of alcohol or propylene glycol-containing products)

Cost-effectiveness

- While the acquisition cost of FDX is much higher than VAN, this may be offset by lower costs of treating recurrence (assuming the recurrence rate is lower with FDX). Several cost-effectiveness analyses have found FDX to be cost-effective or cost-saving vs. VAN, particularly for patients at high risk for recurrence or for first recurrence.[11-13,26]
- Many of these were industry funded, and other analyses suggested VAN may be more cost-effective for initial episodes and that FMT may be more cost-effective than FDX for recurrence, particularly in patients with multiple recurrences.[13,27-29]
- Application of these cost-effectiveness analyses to VHA is difficult as costs vary and outcomes from VHA studies fail to show differences in recurrence which is necessary for FDX to be cost-effective. Still, FDX is likely to be cost-effective in first recurrence

Place in therapy

- Compared to VAN, in 3 of 4 blinded RCTs, FDX was associated with increased rates of sustained cure 30 days post-treatment, lower rates of recurrence, with no significant differences in initial clinical cure, safety events, and mortality for

non-fulminant CDI and is a recommended first-line treatment option in 2021 guidelines from IDSA/SHEA and ACG, including initial, recurrent, non-severe, and severe, non-fulminant episodes.

- In contrast, a 4th RCT and real-world retrospective cohort studies suggest the difference may be less marked with real-world use, and in the VA population. Both sets of guidelines list VAN as an acceptable first line alternative for first episodes of CDI, although the IDSA/SHEA guidelines suggest FDX over VAN.
- FDX does not currently have a role in fulminant CDI or in patients with ileus as these patients were excluded from clinical trials.
- The cost-effectiveness of FDX as a first line agent over VAN isn't clear but FDX is likely to be cost-effective in patients at high-risk for recurrence, despite the higher acquisition cost over VAN.
- In patients initially treated with VAN who experience recurrence, FDX is also an appropriate choice for treatment of first recurrence, although for subsequent recurrences, some data suggest FMT may be a more cost-effective treatment alternative, if available.
- There is extremely limited data about additional benefit of FDX over VAN when bezlotoxumab is used to decrease risk of recurrence as nearly all patients in the RCTs of bezlotoxumab were on VAN or MTZ.
- FDX is generally not appropriate:
    - In those with a history of hypersensitivity reaction to fidaxomicin for another macrolide antibiotic.
    - For the treatment of systemic infections.
    - For the treatment of asymptomatic *C. difficile* colonization
- Good antimicrobial and diagnostic stewardship can offset costs associated with CDI treatment by decreasing antibiotics associated with high risk of CDI, preventing treatment of asymptomatic colonization or based on symptoms without confirmation of CDI as a cause of diarrhea.

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