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NCCN Guidelines Panel: Prevention and Treatment of Cancer-Related Infections

On behalf of Cubist Pharmaceuticals, I respectfully request the *NCCN Prevention and Treatment of Cancer-Related Infections* Panel to review the enclosed data supporting the inclusion of fidaxomicin in both the treatment pathway and table for *C. difficile*-associated diarrhea (CDAD).

Specific Changes Requested: Inclusion of fidaxomicin as a therapeutic option for the treatment of CDAD by: (1) adding fidaxomicin to the FEV-7 *Abdominal Pain, Perirectal Pain, Diarrhea, Urinary Tract Symptoms* diarrhea pathway for the treatment of suspected *C. difficile*; and (2) adding fidaxomicin to the FEV-A *Antibacterial Agents: Gram-positive Activity* table.

FDA Indication and Usage: DIFICID (fidaxomicin) is a macrolide antibacterial indicated in adults (≥ 18 years of age) for treatment of CDAD.

Rationale: Serious consequences following an episode of CDAD in patients with cancer have been reported. These include toxic megacolon, ileus, the development of graft-versus-host disease (GVHD) and/or bloodstream infection, and a delay in the initiation of chemo and/or radiotherapy. As stated in the US FDA approved product labeling, a 10 day course of fidaxomicin demonstrated superior sustained clinical response (defined as clinical response with no subsequent recurrence or death 25 days following the end of treatment) versus oral vancomycin in two multicenter, randomized, controlled trials of 1105 patients (modified intent-to-treat population) (DIFICID Prescribing Information 2014, Louie 2011, Cornely 2012). When specifically evaluating patients with cancer, subanalyses of these data as well as an independent trial support the enhanced sustained clinical response observed following fidaxomicin treatment (Cornely 2013, Esmaily-Fard 2014). In addition, in two recent economic models fidaxomicin has demonstrated cost-effectiveness when compared to vancomycin (Heimann 2014, Broderick 2014). We request broader inclusion of fidaxomicin within the *NCCN Prevention and Treatment of Cancer-Related Infections* guidelines due to less recurrence and superior sustained clinical response over traditional therapies.

The 2013 CDC report *Antibiotic Resistance Threats in the United States* categorizes *C. difficile* as one of only three microorganisms labeled as the highest threat level of urgent, noting 250,000 infections, 14,000 deaths, and \$1 billion in excess medical costs annually. Effective treatment of *C. difficile* infection (CDI) can be challenging; in two recent studies of patients with concomitant hematologic malignancies and CDI, 61.0% and 49.3% of patients experienced CDI treatment failure (Yoon 2014, Parmar 2014, respectively). Furthermore, in Parmar and colleagues' study, 20.5% of patients had recurrent CDI.

Sustained clinical response of CDI treatment is critical, particularly since this infection can cause deleterious outcomes in patients with cancer. Multiple studies have shown a statistically significant relationship between early CDI and subsequent development of GVHD in hematopoietic stem cell transplant (HSCT) recipients versus controls (Dubberke 2010, Alonso 2012, Trifilio 2013; all p -values < 0.05). Patients with concurrent cancer and CDAD were more likely to develop a bloodstream infection before hospital discharge versus controls ($p < 0.001$) and those with

severe CDAD were at an increased risk of death at 180 days (Dubberke 2010). CDAD has also been shown to delay administration of oncologic therapy. In a study of patients hospitalized for radiooncological treatment, 42% of patients had interruptions to their planned radiotherapy, 62% of patients had their chemotherapy discontinued, and 12% of patients died (Hautmann 2011).

Version 1.2013 of the *NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections* summarized some of the existing fidaxomicin data available at that time. An updated summary of key fidaxomicin data includes:

Phase III Trial Results (n = 1105; Trial 1 = Louie 2011, Trial 2 = Cornely 2012)

- Clinical cure (*i.e.*, clinical response) with fidaxomicin was non-inferior to vancomycin (Trial 1: 88.2% vs. 85.8%; Trial 2: 87.7% vs. 86.8%)
- Recurrence was significantly decreased with fidaxomicin vs. vancomycin (Trial 1: 15.4% vs. 25.3%, $p=0.005$; Trial 2: 12.7% vs. 26.9%, $p=0.0002$)
- Sustained clinical response (*i.e.*, global cure) was superior with fidaxomicin vs. vancomycin (Trial 1: 74.6% vs. 64.1%, $p=0.006$; Trial 2: 76.6% vs. 63.4%, $p=0.001$)

Subanalysis of Phase III Data: Patients with Cancer (n = 187; Cornely 2013)

- Sustained clinical response significantly higher with fidaxomicin vs. vancomycin (73.6% vs. 52.1%, $p=0.003$; OR = 2.56; 95% CI: 1.37 to 4.77).
- Shorter time to resolution of diarrhea with fidaxomicin vs. vancomycin (74 hours vs. 123 hours, $p=0.045$)

Subanalysis of Phase III Data: Patients receiving Concomitant Systemic Antibiotics (n = 275; Mullane 2011)

- Clinical cure (*i.e.*, clinical response) significantly higher with fidaxomicin vs. vancomycin (90.0% vs. 79.4%; $p=0.04$)
- Fidaxomicin significantly decreased recurrence (16.9% vs. 29.2%; $p=0.048$)
- Sustained clinical response significantly improved with fidaxomicin vs. vancomycin (72.7% vs. 59.4%, $p=0.02$)

Retrospective evaluation of fidaxomicin use at MD Anderson Cancer Center (n = 22; Esmaily-Fard 2014)

- Evaluated recurrent CDI (n = 16) and CDI refractory to both metronidazole and vancomycin (n = 6)
- Majority of patients (86%) were on concomitant antimicrobials during CDI treatment
- Clinical response observed in 91% of patients; sustained clinical response in 82%

In Version 1.2013, metronidazole is recommended for treatment of CDI over oral vancomycin in non-severe cases, partly due to the risk of selecting for vancomycin-resistant enterococcus (VRE) upon vancomycin exposure. However, recent data from a multicenter, randomized, controlled trial (n=537) showed that clinical cure following metronidazole was inferior to vancomycin for all cases of CDI (72.7% vs. 81.1%, $p=0.02$) and not just in patients with severe disease (Johnson 2014). A recent meta-analysis (Cornely 2014) compared fidaxomicin with metronidazole through indirect analyses. The likelihood of recurrence was significantly lower (OR = 0.42 [95% CI: 0.18 – 0.96]) and sustained clinical response rates significantly higher (OR = 2.55 [1.44 -4.51]) with fidaxomicin. Additionally, in a substudy of patients from the first Phase III trial, those receiving fidaxomicin were less likely than those treated with vancomycin to acquire VRE colonization during CDI treatment (7% vs. 31%, $p<0.001$). (Nerandzic 2012).

The totality of the data presented demonstrate the serious consequences of CDAD and the shortcomings of traditional therapies currently listed within the FEV-7 NCCN pathway. Fidaxomicin is an important therapeutic option for the treatment of CDAD in patients with cancer. We appreciate your consideration for inclusion of fidaxomicin within the treatment pathway and table.

Sincerely,



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