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

On behalf of Merck & Co., I respectfully request the NCCN Guidelines Prevention and Treatment of Cancer-Related Infections Panel to review the enclosed data for possible inclusion of ZINPLAVA[™] (bezlotoxumab) to prevent recurrence of *Clostridium difficile* infection (CDI) in adults who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence.

Specific Changes: Consider recommending in the 2019 guidelines that bezlotoxumab be given during antibacterial treatment of CDI to prevent recurrence of CDI in adult patients with cancer.

FDA Approval: The submitted use is consistent with the FDA approved indication. ZINPLAVA was approved by the FDA on October 21, 2016 to reduce recurrence of *Clostridium difficile* infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence. Patients with cancer who have an episode of CDI are considered to be at a high risk for CDI recurrence.

Rationale: In subgroup analyses of participants enrolled in the two phase 3 clinical trials with a cancer diagnosis, those who received bezlotoxumab plus CDI antibacterial therapy (SOC) had lower rates of recurrent CDI compared with those who received placebo plus SOC (hematologic malignancy: absolute risk reduction (ARR) -19.4 % (95% CI -38.1, -0.7); malignant solid tumor: ARR -9.2% (95% CI -20.7, 2.7).

The following prescribing information and articles are submitted in support of this proposed change.

1. ZINPLAVA [US prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; 2016.
<https://www.merckconnect.com/>
2. Cornely OA, Mullane KM, Bouza E, et al. Impact of bezlotoxumab on outcomes associated with *Clostridium difficile* infection in MODIFY I/II participants with hematologic malignancy. Poster P0358 presented at: European Congress of Clinical Microbiology and Infectious Disease; April 21-24, 2018; Madrid, Spain. This poster presents the baseline characteristics and outcome analysis for participants with a hematologic malignancy from the two bezlotoxumab phase 3 randomized trials (MODIFY I/II). Bezlotoxumab treated patients had significantly lower rates of CDI recurrence versus those who received placebo (14.0% vs 33.3%). Additionally, lower 30-day CDI-associated rehospitalizations (4.3% vs 11.6%) and lower 90-day mortality (9.3% vs 14.5%) were observed in the bezlotoxumab group compared with the placebo group.

3. Mullane KM, Cornely OA, Birch T, et al. Reduction of recurrent *Clostridium difficile* infection and impact on outcomes in participants with a solid tumor in MODIFY I/II treated with bezlotoxumab. Poster P0359 presented at: European Congress of Clinical Microbiology and Infectious Disease; April 21-24, 2018; Madrid, Spain. This poster presents the baseline characteristics and outcome analysis for participants with a solid tumor from the two bezlotoxumab phase 3 randomized trials (MODIFY I/II). Bezlotoxumab treated participants had lower rates of CDI recurrence (20.4% vs 29.5%), 30-day CDI-associated rehospitalization (5.5% vs 10.2%), and lower 90-day mortality (10.5% vs 15.6%) versus those who received placebo.
4. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. *N Engl J Med* 2017;376:305-317. This publication presents the results of the two pivotal phase 3 randomized clinical trials (MODIFYI/II) in participants with primary or recurrent CDI who were receiving antibacterial treatment for CDI. In each trial, the rate of recurrent CDI was significantly lower in participants that received bezlotoxumab compared with those that received placebo, and bezlotoxumab had a safety profile similar to that of placebo.
5. Gerding DN, Kelly CP, Rahav G, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection in patients at increased risk for recurrence. *Clin Infect Dis* 2018; 67:649-656. This publication is an analysis of the participants who received bezlotoxumab or placebo in the two pivotal phase 3 randomized clinical trials (MODIFYI/II) further categorized based on known risk factors for rCDI or CDI-related adverse outcomes. This analysis had been prespecified in the statistical analysis plan at the time of protocol development.

Sincerely,



Diana Nurutdinova, MD