On behalf of Jazz Pharmaceuticals, I respectfully request the NCCN B-Cell Lymphomas Panel to review the enclosed FDA approved label and clinical studies in support of the inclusion of DEFITELIO (defibrotide sodium [defibrotide]) as the treatment of hepatic veno-occlusive disease (VOD) in B-cell lymphoma.

FDA Clearance: DEFITELIO (defibrotide sodium) is indicated for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation (HSCT).

Suggested Changes: We respectfully ask the NCCN Panel to consider adding the following:

NHODG-B 3 of 3: New section

“Hepatic veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS)

- Hepatic VOD is a rare but life-threatening complication following hematopoietic stem cell transplant (HSCT) or chemotherapy without HSCT:
  - Defibrotide for treatment of patients who develop hepatic VOD.
  - Treatment with defibrotide has been shown to result in a 38% to 49% survival rate at 100 days after HSCT in patients with VOD with multi-organ dysfunction (MOD), compared with a historical control rate of 21% to 31%. In 488 patients with VOD without MOD post HSCT, from a large expanded access protocol, defibrotide therapy resulted in 69% survival at 100 days.
  - In patients who developed VOD post-chemotherapy without HSCT, defibrotide therapy resulted in 66% survival with MOD and 81% survival without MOD at 70 days post initiation of defibrotide.

Rationale Summary:
Defibrotide is the first and only FDA-approved therapy for treatment of hepatic VOD with renal or pulmonary dysfunction following HSCT, a rare and life-threatening liver complication that can occur following HSCT or chemotherapy. Although rare, hepatic VOD with multiorgan dysfunction is associated with a very high mortality rate of up to 80%. Use of defibrotide resulted in 38% to 49% survival at 100 days after HSCT in patients with MOD, in a wide variety of underlying malignancies, compared with a historical control rate of 21 to 31%. In 488 patients with VOD without MOD post HSCT from a large expanded access protocol, defibrotide therapy resulted in 69% survival at 100 days. Based on a posthoc analysis from a large expanded access protocol, in patients who developed VOD after a variety of chemotherapy regimens without HSCT, use of defibrotide resulted in 74% survival at 70 days. Inclusion of defibrotide as a therapy can provide an effective option to patients affected by this frequently fatal condition.
Published Literature Support:
Defibrotide is not approved by the FDA for use in patients with hepatic VOD without MOD following HSCT nor in patients who developed VOD post-chemotherapy without HSCT.

**Post-HSCT**
Defibrotide was studied in 2 prospective trials and an expanded access study in patients diagnosed with hepatic VOD after HSCT. In the phase 3 study, defibrotide was administered intravenously at 25 mg/kg daily in 4 divided doses, infused over 2 hours every 6 hours for a minimum of 21 days. The study involved a total of 134 patients.

Defibrotide treatment resulted in 38.2% survival at day +100 post-HSCT in 102 patients with established hepatic VOD and MOD, compared with 25.0% in 32 historical controls identified out of 6867 medical charts of HSCT patients by blinded independent reviewers (estimated difference adjusted for propensity score=23%, 95.1% CI, 5.2-40.8; P=0.0109, propensity-adjusted analysis). Observed day +100 complete response rates equaled 25.5% for defibrotide and 12.5% for controls (estimated difference adjusted for propensity score=19%, 95.1% CI, 3.5-34.6; P=0.0160). Hypotension was the most common AE in both groups (39.2% with defibrotide, 50% for historical controls). Overall, there was no difference in the incidence of common hemorrhagic AEs (64% with defibrotide and 75% with historical control).

Under a broad expanded-access treatment protocol involving 1000 patients with VOD and with or without MOD post HSCT, day +100 survival was 58.9% (95% CI, 55.7%-61.9%) in patients treated with defibrotide. Among 512 patients with MOD, 49.5% (95% CI, 45.0%-53.0%) were alive at day +100 post-HSCT. In 488 patients without MOD, the +100 day post-HSCT survival was 68.9% (95% CI, 64.5%-72.9%). These results were consistent with an earlier phase 2 study that enrolled 149 patients with VOD and MOD, with an overall complete response rate of 46% and day +100 post-HSCT survival rate of 42%. The expanded-access treatment protocol data reported grade ≥3 treatment-related AEs in 3% of patients with no treatment-related deaths. The incidence of grade ≥3 expected AEs was 55% with the most common being renal failure (31%), hypotension (29%), hypoxia (26%), and pulmonary AEs (22%). Defibrotide-related toxicity resulting in treatment discontinuation occurred in only 4% of patients.

**Post-chemotherapy without HSCT**
In a posthoc analysis, the efficacy of defibrotide post-chemotherapy without HSCT has also been studied under the expanded access protocol. A total of 82 patients received defibrotide within 30 days of starting a variety of chemotherapy regimens without HSCT. The 70-day Kaplan-Meier estimate survival was 74.1% (65.8% and 81.3% in patients with and without MOD, respectively). Further exploratory analysis in this subset of patients suggests that earlier defibrotide initiation post-VOD diagnosis was associated with improved survival.

Sincerely,

Francois Di Trapani
Vice President Global Scientific Affairs

**References (enclosed):**
1. DEFITELIO prescribing information. 2016. Jazz Pharmaceuticals, Inc.