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NCCN Hematopoietic Cell Transplantation Panel

Request for review of clinical data for DEFITELIO® (defibrotide sodium [defibrotide]) in the NCCN Clinical Practice Guidelines in Oncology® for Hematopoietic Cell Transplantation

On behalf of Jazz Pharmaceuticals, I respectfully request the NCCN Hematopoietic Cell Transplantation Panel to review the enclosed FDA approved label and clinical studies in support of the inclusion of DEFITELIO® as treatment for hepatic veno-occlusive disease (VOD) following hematopoietic stem-cell transplantation (HSCT*).[1-5] This topic is not addressed in the current transplant guidelines; therefore, I am requesting an additional section to be added on the management of hepatic VOD, a potentially life-threatening complication of transplant.

FDA Clearance: DEFITELIO is indicated for the treatment of adult and pediatric patients with hepatic VOD, also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following HSCT.[1]

Suggested Key Points:

- Hepatic VOD, also called SOS, is a potentially life-threatening complication of HSCT.[2] Untreated hepatic VOD/SOS with multi-organ dysfunction (MOD) is associated with >80% mortality.
- Defibrotide is the first and only FDA-approved treatment for patients who develop hepatic VOD with renal or pulmonary dysfunction following HSCT.[1]
- In a Phase 3 prospective study, defibrotide resulted in a 38.2% survival rate at 100 days after HSCT in patients with VOD and MOD, compared with a historical control rate of 25.0%.[3]
- In an earlier Phase 2 prospective study, defibrotide resulted in a 42% survival rate at 100 days in patients with VOD and MOD following HSCT.[4]
- In a large, expanded-access protocol including 1000 patients with VOD post-HSCT with or without MOD, defibrotide therapy resulted in 49.5% and 68.9% estimated survival at 100 days, respectively, and an estimated overall survival of 58.9% at 100 days.[5]

Rationale and Supporting Literature:

The incidence of VOD/SOS reported in the contemporary literature ranges from 10% to 20% (up to 60% in a subset of pediatric patients) after allogeneic hematopoietic cell transplantation using myeloablative conditioning to 0% to 10% following reduced intensity conditioning.[6] Approximately 30% to 50% of patients diagnosed with hepatic VOD developed MOD.[7] Defibrotide was studied in two prospective trials and an expanded access study in patients diagnosed with hepatic VOD after HSCT.[3-5] Historical data

*HSCT acronym used to be consistent with prescribing information and clinical studies.

reported the association of hepatic VOD and MOD with a very high mortality rate greater than 80% at 100 days in untreated patients receiving supportive care alone.[2]

In a prospective 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.[3] Defibrotide treatment resulted in 38.2% survival at 100 days 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 complete response rates at 100 days 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 adverse event (AE) in both groups (39.2% with defibrotide, 50% for historical controls). Defibrotide was generally well tolerated in this study. The incidence of common hemorrhagic AEs was similar between defibrotide and control groups (pulmonary alveolar: 11.8% and 15.6%; gastrointestinal: 7.8% and 9.4%). In an earlier Phase 2 prospective study of 149 treated patients with VOD and MOD following HSCT, defibrotide resulted in 46% complete response and 42% survival at 100 days.[4]

A large expanded-access treatment program (T-IND) for defibrotide included 1000 post-HSCT patients with VOD, with or without MOD. [5] Defibrotide treatment resulted in 58.9% (95% CI, 55.7%-61.9%) estimated survival at 100 days. Among 512 patients with MOD, estimated survival at 100 days post-HSCT was 49.5% (95% CI, 45.0%-53.8%). In 488 patients without MOD, estimated survival at 100 days post-HSCT was 68.9% (95% CI, 64.5%-72.9%). An exploratory *post hoc* analysis found a higher Day +100 survival in patients who had earlier initiation of defibrotide (*P*<0.001). Treatment-related AEs (TRAEs) were reported in 210 patients (21.0%) with a slightly higher incidence in patients with MOD compared to patients without MOD (23.0% vs. 18.9%, respectively). TRAEs occurring in ≥2% of patients included pulmonary hemorrhage (4.6%), gastrointestinal hemorrhage (3.0%), epistaxis (2.3%), and hypotension (2.0%). TRAEs led to treatment discontinuation in 124 patients (12.4%) and death in 28 patients (2.8%).

In a pooled analysis of defibrotide treatment of VOD with or without MOD in 2598 adult and pediatric patients, the estimated Day +100 overall survival was 54%.[8] Defibrotide therapy resulted in 41% and 70% estimated survival at 100 days in patients with and without MOD, respectively.

Recently, consensus statements from US and international expert groups have recommended defibrotide for the treatment of VOD following HSCT.[6,9,10]

In summary, we request your consideration of defibrotide in the NCCN Guidelines for Hematopoietic Cell Transplantation. Inclusion of defibrotide as a therapy for VOD following HSCT can provide an effective option for patients affected by this life-threatening condition.

Sincerely,

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Vice President Global Scientific Affairs

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