Jazz Pharmaceuticals

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NCCN Hematopoietic Cell Transplantation Panel

Request for review of clinical data for DEFITELIO® in the inaugural 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[1] and clinical studies[2-5] in support of the inclusion of DEFITELIO® (defibrotide sodium [defibrotide]) as treatment for hepatic veno-occlusive disease (VOD) following hematopoietic stem-cell transplantation (HSCT).

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 HSCT.[1]

Suggested Key Points:

- Although rare, hepatic VOD with multiorgan dysfunction is associated with a very high mortality rate greater than 80% in untreated patients.[2]
- Defibrotide is the first and only FDA-approved treatment for patients who develop hepatic VOD with renal or pulmonary dysfunction following HSCT.[1]
- In two prospective trials, defibrotide resulted in a 38% to 42% survival rate at 100 days after HSCT in patients with VOD with multi-organ dysfunction (MOD), compared with a historical control rate of 25%.[3,4]
- 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 survival of 58.9% at 100 days.[5]

Rationale and Supporting Literature:
Defibrotide was studied in two prospective trials[3,4] and an expanded access study[5] in patients diagnosed with hepatic VOD after HSCT. In a pooled analysis of defibrotide treatment of VOD with or without MOD in 2598 adult and pediatric patients, the estimated day +100 survival was 54%.[6] Historical data reported the association of hepatic VOD with 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,[3] 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. 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 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 adverse events was similar between defibrotide and control groups (pulmonary alveolar: 11.8% and 15.6%; gastrointestinal: 7.8% and 9.4%).[3] In an earlier phase 2 prospective study of 149 treated patients with VOD with MOD following HSCT, defibrotide resulted in 46% complete remission 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 ($P < 0.001$). 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). Treatment-related AEs occurring in ≥2% of patients included pulmonary hemorrhage (4.6%), epistaxis (2.3%), and hypotension (2.0%). TRAEs led to treatment discontinuation in 124 patients (12.4%) and death in 28 patients (2.8%).[5]

In summary, we request your consideration of defibrotide during the development of the inaugural NCCN Guidelines for HSCT. Inclusion of defibrotide as a therapy for VOD following HSCT can provide an effective option for patients affected by this frequently fatal condition.

Sincerely,

Francois Di Trapani
Vice President Global Scientific Affairs

References (enclosed):

1. DEFITELIO prescribing information. 2016. Jazz Pharmaceuticals, Inc.
2. Coppell J, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant. 2010;16(2):157-168.
3. Richardson PG, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood. 2016;127(13):1656-65.
4. Richardson PG, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. Biol Blood Marrow Transplant. 2010;16(7):1005-1017.
5. Kernan NA, et al. Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome. Br J Haematol. 2018;181(6):816-827.
6. Richardson PG, et al. Systematic review of defibrotide studies in the treatment of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS). Bone Marrow Transplant. 2019 Feb 25. [Epub ahead of print]