CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208114Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	3 March 2016
From	R. Angelo de Claro, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 208114 Original
Applicant	Jazz Pharmaceuticals, Inc.
Date of Submission	31 July 2015
PDUFA Goal Date	31 March 2016
Proprietary Name / **Established (USAN) names**	Defitelio / Defibrotide sodium
Dosage forms / Strength	Injection: 200 mg/2.5 mL in a single patient-use vial
Proposed Indication	Treatment of hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with [redacted] (b) (4) dysfunction following hematopoietic stem-cell transplantation (HSCT)
Intended Populations	Adult and pediatric populations
Recommendation on Regulatory Action	*Approval, pending final report from Facilities review*
Recommended Indication	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)

Material Reviewed/Consulted	Reviewer
Clinical Review	Tanya Wroblewski / Donna Przepiorka
Statistical Review	Cindy Gao / Yuan-Li Shen
Pharmacology Toxicology Review	Brenda Gehrke / Ramadevi Gudi / Christopher Sheth / Haleh Saber
CMC Review	Primary Reviewers: Refer to CMC Review Application Technical Lead: Anamitro Banerjee
Clinical Pharmacology Review	Guoxiang Shen / Bahru Habtemariam Jee Eun Lee / Nitin Mehrotra
OSI/DGCPC	Anthony Orencia / Janice Pohlman
OSE/DRISK	Naomi Redd
OSE/DMEPA	Nicole Garrison / Michelle Rutledge / Yelena Maslov

1. Benefit-Risk Assessment

Defitelio (defibrotide sodium) is a new molecular entity that is a polydisperse mixture of predominately single-stranded polydeoxy-ribonucleotides derived from porcine intestinal tissue. Defibrotide sodium demonstrates profibrinolytic properties in vitro but the exact mechanism of action has not been fully elucidated.

Hepatic veno-occlusive disease (VOD) with evidence of multi-organ dysfunction (renal or pulmonary) is a life-threatening condition that can occur after hematopoietic stem cell transplantation (HSCT). The mortality rate of hepatic VOD with multi-organ dysfunction is over 80% (Coppell et al. 2010). There are currently no approved therapies for the proposed indication, and the current standard of care consists of supportive therapy. Despite improvements in supportive care for transplantation over the past decade, the survival for patients with hepatic VOD with multi-organ dysfunction has not improved.

The efficacy of defibrotide sodium for the proposed indication was established based on the results of the following clinical trials: Study 2005-01 (prospective trial), Study 99-118 (Phase 2 dose-finding trial), and Study 2006-05 (expanded access protocol). The Day +100 survival rates for patients treated with DEFITELIO ranged from 38% to 45% based on the 3 clinical trials. Based on published reports and analyses of patient level data for individuals with hepatic VOD with renal or pulmonary dysfunction who received supportive care or interventions other than DEFITELIO, the expected Day +100 survival rates are 21% to 31%.

Defibrotide sodium appears to have reasonable safety profile when assessed in the context of the treatment of a life-threatening disease with no approved therapy options; however, the safety assessment is limited by the lack of complete controlled safety data. There is a high rate of adverse reactions in patients being treated for hepatic VOD with multi-organ dysfunction using the proposed dose-schedule of defibrotide sodium, but there is no consistent signal that any of the events were caused specifically by defibrotide sodium. The published reports of safety of defibrotide sodium in other populations and the review of the postmarketing reports are consistent with the relative tolerability of defibrotide sodium in the VOD trials. Hemorrhage, hypersensitivity, and pharmacologic interaction with anticoagulants and fibrinolytic therapies are safety concerns that can be mitigated by appropriate warnings, contraindications and instructions for patient selection and dose modifications in the Prescribing Information. Overall, the clinical benefit of defibrotide sodium remains favorable in light of the residual concern of the lack of a complete safety data from a randomized trial.

The clinical trials enrolled 66 pediatric patients in the following age groups: 22 infants (1 month up to less than 2 years), 30 children (2 years up to less than 12 years), and 14 adolescents (12 years to less than 17 years). The efficacy and safety outcomes were consistent across pediatric and adult patients in both Study 2005-01 and Study 99-118.

I recommend traditional approval for the following indication: 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). All review teams recommend approval.

The recommended dose and schedule for Defitelio is 6.25 mg/kg intravenously every 6 hours for at least 21 days, and dosing may be continued until VOD resolution up to 60 days of treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Toxic injury to hepatic endothelial cells from high dose chemotherapy can lead to hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive syndrome (SOS). The clinical symptoms include hepatomegaly, ascites, and weight gain. Most cases of hepatic VOD occur after hematopoietic stem cell transplantation (HSCT) although hepatic VOD can occur after chemotherapy or other toxic insults to the liver. The incidence of hepatic VOD varies between studies due to baseline risk factors, type of transplantation, conditioning regimen, and the criteria used for diagnosis. The incidence has been estimated at 14% with rates ranging from 5% to as high as 60% (Coppell 2010). Hepatic VOD with multi-organ dysfunction occurs in <2% of patients after HSCT and is a life-threatening condition (> 80% mortality rate) (Coppell 2010).	Hepatic veno-occlusive disease (VOD) is a rare condition that most often occurs after hematopoietic stem cell transplantation (HSCT). Hepatic VOD with multi-organ dysfunction is a serious and life-threatening medical condition. Incidence of hepatic VOD varies between studies in the literature.
Current Treatment Options	There are currently no approved therapeutic agents available for the treatment of hepatic VOD with renal or pulmonary dysfunction following HSCT. Treatment generally consists of supportive care. Despite improvements in supportive care for HSCT over the past decades, the mortality for patients with hepatic VOD with multi-organ dysfunction has not improved.	There is an unmet medical need for patients for VOD, specifically patients with hepatic VOD with multi-organ dysfunction.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	The efficacy of defibrotide sodium for the proposed indication was established based on the results of the following clinical trials: Study 2005-01 (prospective trial), Study 99-118 (Phase 2 dose-finding trial), and Study 2006-05 (expanded access protocol). Study 2005-01 was a prospective trial that enrolled 102 patients with hepatic VOD with renal or pulmonary dysfunction after allogenic or autologous HSCT. Efficacy results evaluated by Day +100 survival after transplantation demonstrated an observed survival rate of 38% (95% CI: 29, 48) in patients treated with 25 mg/kg/day defbrotide sodium. In Study 99-118, 75 patients with VOD and multi-organ dysfunction who received 25 mg/kg/day defibrotide sodium demonstrated a Day +100 survival of 44% (95% CI: 33,55). In Study 2006-05, 351 patients with VOD with multi-organ dysfunction who received 25 mg/kg/day defibrotide sodium showed a Day +100 post-HSCT survival of 45% (95% CI: 41,51). The statistical team raised concerns of the validity of the propensity score adjusted analysis for small sample size and a variation of treatment effect estimates when varying propensity defined strata were used. (b) (4) The primary secondary efficacy endpoint for Study 2005-01 was complete response (CR) by Day +100 post-HSCT. (b) (4)	The totality of Day +100 survival findings across the three trials provide substantial evidence for the efficacy of defibrotide sodium for the following indication: 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). The results will be presented in a descriptive approach in the labeling. (b) (4) (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	The safety data for this NDA review included 1894 individuals exposed to defibrotide sodium in seven sponsored-studies or trials of treatment of VOD, treatment of other disorders, and prevention of VOD or evaluations of PK or PD. However, none of the trials in patients with VOD collected all treatment emergent adverse events. In order to make the best safety assessment on adverse events at the proposed dose data was pooled from 176 subjects with hepatic VOD and multi-organ dysfunction after HSCT treated with defibrotide sodium 6.25 mg/kg intravenously every 6 hours in Studies 2005-01 and 99-118. This group is the Selected Safety Population (SSP). Mortality within 30 days after the last dose of defibrotide sodium was 55% in the SSP and no deaths could be clearly ascribed to defibrotide sodium. The most common (≥ 10%) SAEs in the SSP were multi-organ failure, hypotension, respiratory failure, and renal failure. The most common (≥10%) TEAES in the SSP were hypotension, diarrhea, multi-organ failure, vomiting, renal failure, nausea, epistaxis, respiratory failure, hypertension, hypoxia, and pyrexia. Additionally, 25% of patients had a grade≥3 elevation in aPTT (activated partial thromboplastin time) but the elevation was not consistent over time and no dose-dependent increase in PTT was observed in Study 99-118. Additional support for the safety of defibrotide sodium comes for two large (< 1000 subjects) trials evaluating the efficacy of defibrotide sodium 200 mg intravenously 4 times day for thromboembolic prophylaxis after surgical procedures. The incidences of adverse reactions reported were <1% and 1.3%. The safety database does not include sufficient number of subjects (only 1) aged 65 and older to determine whether they respond differently from younger subjects. Study 2005-01 and 99-118 enrolled 66 pediatric patients in the	Defitelio (defibrotide sodium) appears to have reasonable safety profile when assessed in the context of the treatment of a life-threatening disease with no approved treatment options however the safety assessment is limited by the lack of complete controlled safety data. There is a high rate of adverse reactions in patients being treated for hepatic VOD with multi-organ failure using the proposed dose-schedule but there is no consistent signal that any of the events were caused specifically by defibrotide sodium. Published reports of safety of defibrotide sodium in other populations and review of the postmarketing reports are consistent with the relative tolerability of defibrotide sodium in VOD trials. The clinical benefit of defibrotide sodium remains positive in light of the residual concern of the lack of a complete safety data from a randomized trial. The best available adverse event information to assess safety of the proposed dose in the intended population was pooled data from 176 subjects with hepatic VOD and multi-organ dysfunction after HSCT treated with defibrotide sodium 6.25 mg/kg every 6 hours. The safety analysis of the Selected Safety Population revealed no unexpected events for patients with VOD with multi-organ dysfunction after HSCT. There were no substantial and consistent

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	following age groups: 22 infants (1 month up to less than 2 years), 30 children (2 years up to less than 12 years), and 14 adolescents (12 years to less than 17 years). The safety and efficacy outcomes were consistent across pediatric and adult patients in both clinical trials. Hemorrhage is a clear potential adverse reaction for defibrotide sodium based on its pharmacologic effects and apparent dose-toxicity relationship. Hypersensitivity is a second potential adverse reaction for defibrotide sodium and there were no immunogenicity studies performed. No formal drug-drug interaction studies were conducted by the Applicant. The pharmacological activity of defibrotide sodium suggests potential to enhance the activity of fibrinolytic agents. There were no unexpected serious adverse events reported in the postmarketing setting since the approval of defibrotide sodium in Europe in 2013 for treatments of severe hepatic VOD following HSCT.	adverse effects of defibrotide sodium when used as treatment or prevention of VOD in the HSCT recipients in comparison to safety outcomes in the respective control groups as assessed by the Applicant. The additional safety data from two large trials in a thromboembolic prophylaxis indication supports this conclusion. To ensure that safe use can be recapitulated in practice, the Prescribing Information should contain at least the same levels of controls as the protocols with regard to warnings, patient selection, monitoring, and treatment interruption for bleeding or invasive procedures. No important differences are expected in how defibrotide sodium was studied and administered in the clinical trials versus its expected and current use in the post-market setting.
Risk Management	Hemorrhage, hypersensitivity and pharmacologic interaction with anticoagulants and fibrinolytic therapies are safety concerns that can be addressed through labeling and routine pharmacovigilance. The lack of complete safety data from a randomized trial is a residual concern. A safety postmarketing requirement (PMR) is recommended to assess the safety based on the safety results in a randomized, open-label multi-center clinical trial comparing defibrotide sodium versus best supportive care in the prevention of hepatic VOD in adult and pediatric patients, including all adverse events, laboratory abnormalities, and frequent peri-infusion vital signs. Postmarketing commitments are also recommended to (a) develop	Information in Warnings and Precautions section included in the product labeling adequately address the safety concerns identified during review of this NDA. Two PMRs will be addressed by the Applicant concerning the immunogenicity of Defitelio; milestone dates for the PMRs have been provided by the Applicant. The clinical safety PMR will be addressed by the Applicant in a randomized comparative trial; milestone dates for this study have been

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	sensitive and specific anti-drug binding and neutralizing assays (PMC 1), and (b) evaluate patients' sera for binding and neutralizing antibodies to defibrotide sodium using the validated assays from PMC 1 and submit the data in a final immunogenicity study report. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or routine pharmacovigilance that would warrant consideration for Risk Evaluation and Mitigation Strategy (REMS).	provided by the Applicant.

2. Background

On July 31, 2015, Jazz Pharmaceuticals, Inc. (Applicant) submitted a New Drug Application (NDA) for Defitelio. The Applicant proposed the following indication: Treatment of hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with (b) (4) dysfunction following hematopoietic stem-cell transplantation (HSCT).

Defitelio is a new molecular entity (NME) and is not currently marketed in the U.S. The regulatory history for Defitelio is summarized below:

1980s	Defibrotide was produced in 1983, and oral an injectable formulation developed by Gentium S.p.A.(formerly Crinos-Villa Guardia[Como]-Italy) received marketing authorization(MA) in Italy for prophylaxis of deep-vein thrombosis and treatment of thrombophlebitis(Proclide®, Noravid®).
2000	Phase 2 dose-finding study to treat severe VOD(99-118) enrolled its first patient.
2003	Gentium submitted US IND 62118 for defibrotide to treat severe hepatic VOD.
2009	Italian marketing authorizations for all defibrotide products were withdrawn by Gentium S.p.A. effective April 2009 for commercial reasons.
2009	Pivotal Phase 3 Study in the US for the treatment of hepatic VOD with MOF completed
2011	Gentium submitted NDA (b) (4) however FDA identified issues related to clinical data integrity issues and Gentium withdrew application in August.
2013	Defibrotide (trade name Defitelio®) was granted Marketing authorization by the European Commission for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive syndrome (SOS) in hematopoietic stem cell transplantation therapy.
2014	Gentium was acquired by Jazz Pharmaceuticals. Meetings with the FDA established a path forward for defibrotide development in the US and agreed on the content of a new application. FDA granted rolling review of this NDA in November 2014.
2015	Defibrotide was granted marketing authorization in Israel.
2015	The complete NDA 208114 was submitted to the FDA (July 31, 2015).

Defibrotide has only been available in the US through compassionate use programs since 1997.

Hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive syndrome (SOS) can occur after toxic injury to the liver. The occurrence of VOD is now generally seen in patients who undergo hematopoietic stem cell transplantation. The incidence of VOD varies between studies due to baseline risk factors, type of transplantation, conditioning regimen, and the criteria used for diagnosis. The mean prevalence has been estimated at 14 percent with rates ranging from 5% to as high as 60% (Coppell 2010).

The clinical development of hepatic VOD is characterized by tender hepatomegaly, ascites, jaundice, and elevation of serum bilirubin in the absence of other etiologies that could cause similar signs and symptoms. The onset of hepatic VOD usually occurs in the early post-

transplantation period (within first 1-3 weeks after HSCT) but later presentations can occur. Approximately 50% of patients will develop renal insufficiency and 25% of patients will require hemodialysis. Hepatic VOD with multi-organ failure has a mortality rate of 84% (95% CI: 80%, 89%) within the first 100 days (Coppell 2010, Carreras 2011).

Hepatic venous occlusive disease with evidence of multi-organ dysfunction (renal or pulmonary) is a life-threatening condition that can occur after hematopoietic stem cell transplantation. The mortality rate of hepatic VOD with multi-organ dysfunction is over 80% (Coppell et al. 2010). There are currently no approved therapies for the proposed indication, and current standard of care consists of supportive therapy. Despite improvements in supportive care for transplantation over the past decade, the survival for patients with hepatic VOD with multi-organ dysfunction has not improved.

The primary basis for the efficacy of Defitelio are the results from Study 2005-01 (ClinicalTrials.gov identifier NCT00358501), a prospective trial. Supportive clinical trials include Study 99-118 (ClinicalTrials.gov identifier NCT00003966)(randomized Phase 2 dose-finding trial), and Study 2006-05 (ClinicalTrials.gov identifier NCT00628498) (expanded access protocol).

The safety data for this NDA review included 1894 individuals exposed to Defitelio in seven sponsored studies or trials of treatment of VOD, treatment of other disorders, and prevention of VOD or evaluations of PK or PD. However, none of the trials in patients with VOD collected all treatment emergent adverse events. In order to make the best safety assessment on adverse events of defibrotide at the proposed dose data was pooled from 176 subjects with hepatic VOD and multi-organ dysfunction after HSCT treated with defibrotide 6.25 mg/kg intravenously every 6 hours in Studies 2005-01 and 99-118. This group is the Selected Safety Population (SSP).

CDTL Comment: During the review, CMC team identified USAN nomenclature issues (refer to Section 3 of CDTL review). Several of the primary reviews were finalized (before February 5, 2016) based on USAN term (b) (4) *On February 5, 2016, the Applicant submitted revised labeling based on USAN term "defibrotide sodium".*

3. Product Quality

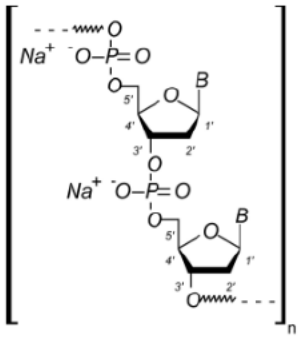
Source: CMC Review

CMC Team Recommendation (12/31/15): The Applicant has provided adequate CMC information. No CMC deficiencies were identified. The labeling should be revised to reflect (b) (4) **the sodium salt as per our current policy. Facility review is pending.**

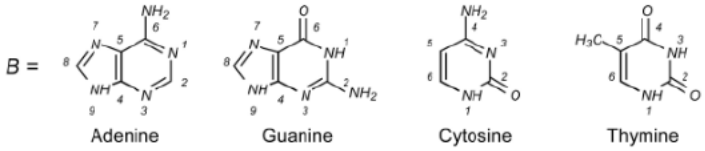
- *General product quality considerations*

  Defibrotide is an oligonucleotide mixture with profibrinolytic properties. The chemical name of defibrotide is polydeoxyribonucleotide, sodium salt. Defibrotide is a polydisperse mixture of predominantly single-stranded (ss) polydeoxyribonucleotide

sodium salts derived from porcine intestinal tissue having a mean weighted molecular weight of 13-20 kDa. The primary structure of defibrotide is shown below.



n = from about 2 to 50



DEFITELIO (defibrotide) injection is a clear, light yellow to brown, sterile, preservative-free solution in a single-patient-use vial for intravenous use. Each milliliter of the injection contains 80 mg of defibrotide and 10 mg of Sodium Citrate, USP, in Water for Injection, USP. Hydrochloric Acid, NF, and/or Sodium Hydroxide, NF, may have been used to adjust pH to 6.8-7.8.

The Applicant provided primary and supporting stability data support the storage of the drug product under controlled room temperature 20-25°C (68-77°F) with excursions permitted to (b) (4) -30° C (59-86°F). The proposed expiration dating period of 36 months for the drug product is supported by the real time (36 months) data from both primary stability batches and supporting stability batches.

- *Facilities review/inspection:* At the time of completion of the CDTL review, the facility review is pending.

- *Other notable issues*: CMC team cited USP <1121> Salt Policy that stipulates that the drug product be labeled with the strength of the active moiety (b) (4) At the Late Cycle Meeting on 29 January 2016, FDA identified two possible options for the Applicant. The first option would be to use a United States Adopted Names (USAN) of defibrotide sodium, and this would allow keeping the proposed dosing of 6.25 mg/kg and strength of 80 mg/mL. (b) (4) (b) (4) (b) (4)

(b) (4) The Applicant plans to change USAN to defibrotide sodium and to keep the existing USAN definition.

CDTL Comment: USAN of defibrotide sodium would be preferred, as this would allow for worldwide consistency of dosing at 25 mg/kg/day ~ 6.25 mg/kg every 6 hours.

4. Clinical Microbiology

Not applicable.

5. Nonclinical Pharmacology/Toxicology

Source: Pharmacology and Toxicology Review

Pharmacology Toxicology Team Recommendation: Approval

- General nonclinical pharmacology/toxicology considerations

  Defibrotide is a sodium salt of a complex of mainly single-stranded polydeoxyribonucleotides derived from porcine intestinal tissue. The pharmacology and toxicology studies reviewed included those that assessed the pharmacodynamics, pharmacokinetics, genotoxicity, safety pharmacology, repeat dose toxicology (continuous and intermittent infusion) in rats and dogs, effects on embryo-fetal development in rats and rabbits and pre- and post-natal development in rats, juvenile animal toxicology in rats, and oral carcinogenicity of defibrotide in mice and rats.

  Hepatic VOD following HSCT involves chemotherapy-induced sinusoidal endothelial cell damage (leading to apoptosis) followed by thrombosis, which may lead to organ dysfunction. The Applicant's studies demonstrated defibrotide ameliorates chemotherapy-induced stress responses of endothelial cells in addition to reversing deleterious effects on fibrinolysis.

  There remains an incomplete understanding of the mechanism of action of defibrotide; (b) (4)

  Target organs of toxicity were identified in a 13-week rat toxicology study, which included adverse findings in the kidneys, liver and lymphoid tissues. Defibrotide also prolonged prothrombin time (PT) in rats, in addition to activated partial thromboplastin time (APTT) in rats and dogs. Defibrotide may have direct effects on coagulation based on the dose-dependent effects of the drug on PT and APTT.

- Carcinogenicity

  No carcinogenicity studies have been conducted with defibrotide administered by the intravenous route and the oral studies were inadequate to conduct an assessment of the potential for carcinogenicity. Defibrotide was not mutagenic in the in vitro bacterial

reverse mutation assay (Ames assay) nor was it clastogenic in an in vivo bone marrow micronucleus assay in rats. Defibrotide was devoid of clastogenic activity in the in vitro chromosomal aberration assay in Chinese hamster ovary cells in the presence or absence of an exogenous metabolic activation system.

- Reproductive toxicology

  The Applicant's proposal for Section 8.1 of the label is consistent with the Pregnancy and Lactation Labeling Rule. Defitelio may cause fetal harm based on findings in animals. Exposure to defibrotide was associated with embryo-fetal toxicity (decreased number of implantations and viable fetuses compared to controls) in pregnant rabbits at doses approximately equivalent to the recommended clinical dose on a mg/m2 basis. Studies of fertility and pre- and postnatal toxicology were not conducted with defibrotide administered by the intravenous route. Defibrotide, given intramuscularly, was tested in non-GLP studies for effects on fertility and pre- and postnatal development; however these studies were not fully reviewed. The repeat dose general toxicology studies included evaluation of reproductive tissues, and there were no effects due to treatment with intravenously administered defibrotide on male or female reproductive organs in studies up to 13-weeks in duration in rats or dogs. The juvenile rat toxicology study revealed a delayed mean age to preputial separation in defibrotide treated males.

- Other notable issues: None

CDTL Comment: I agree with the approach to (b) (4)

6. Clinical Pharmacology

Source: Clinical Pharmacology Review

Clinical Pharmacology Team Recommendation: Approval

- General clinical pharmacology considerations

  The proposed dose of 25 mg/kg/day was selected based on the comparison of efficacy (CR and Day+100 survival) and safety of defibrotide 25 mg/kg/day versus 40 mg/kg/day in patients with severe VOD in the Phase 2 dose finding study 99-118. In this study, there was no difference in efficacy as measured by either CR or survival at Day+100. There was a slightly higher incidence (>4%) of treatment-related TEAEs, treatment-related SAEs, fatal TEAEs, hemorrhage and hypotension TEAEs in the 40 mg/kg/day treatment arm. Although these results did support the selection of 25 mg/kg/day over 40 mg/kg/day for the Phase 3 study, it was not clear if a dose lower than 25 mg/kg/day would provide improved benefit-to-risk ratio. To address this concern, the Applicant collected and analyzed the efficacy data prospectively at doses ranging from 10 mg/kg/day to 80 mg/kg/day in a compassionate use program. The results suggested that survival at Day+100 increased from 36.5% at 10 mg/kg/day to 44.9% at 25 mg/kg/day, then reached

a plateau at higher doses (40 to 80 mg/kg/day), which is consistent with the finding in the Phase 2 dose finding study.

Absorption
After intravenous administration, peak plasma concentrations of defibrotide occur approximately at the end of each infusion.

Distribution
Defibrotide is highly bound to human plasma proteins (average 93%) and has a volume of distribution of 8.1 to 9.1 L.

Elimination
Metabolism followed by urinary excretion is likely the main route of elimination. The estimated total clearance was 3.4 to 6.1 L/h. The elimination half-life of defibrotide is less than 2 hours. Similar plasma concentration profiles were observed in VOD patients after initial and multiple-dose administration of 6.25 mg/kg every 6 hours for 5 days. Therefore, no accumulation is expected following multiple-dose administration.

Metabolism
Though the precise pathway of defibrotide degradation in plasma in vivo is largely unknown, it has been suggested that nucleases, nucleotidases, nucleosidases, deaminases, and phosphorylases metabolize polynucleotides progressively to oligonucleotides, nucleotides, nucleosides, and then to the free 2'-deoxyribose sugar, purine and pyrimidine bases.

The biotransformation of defibrotide was investigated in vitro by incubation with human hepatocytes from donors of different ages and showed that defibrotide does not undergo appreciable metabolism by human hepatocyte cells.

Excretion
After administration of 6.25 mg/kg to 15 mg/kg doses of DEFITELIO as 2-hour infusions, approximately 5-15% of the total dose was excreted in urine as defibrotide, with the majority excreted during the first 4 hours.

- Drug-drug interactions

Pharmacokinetic drug-drug interactions are unlikely at therapeutic dose. Data from in vitro studies using human biomaterial demonstrate that defibrotide does not induce (CYP1A2, CYP2B6, CYP3A4, UGT1A1) or inhibit (CYP1A2, CYP2B6, CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT1A1, UGT2B7) the major drug metabolizing enzymes and is not a substrate or inhibitor of the major drug uptake transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3) or efflux transporters (P-gp and BCRP).

There is some evidence (animal studies, ex vivo human plasma, and healthy volunteers) that defibrotide may enhance the pharmacodynamic activity of heparin and alteplase

- Pathway of elimination

  Refer to metabolism section of "General clinical pharmacology considerations".

- Intrinsic factors

  Age: Pediatric Population
  Insufficient PK data were collected in pediatric patients to draw conclusions.

  Renal Impairment
  The safety, tolerability, and pharmacokinetics of 6.25 mg/kg as 2-hour intravenous infusions of DEFITELIO were evaluated in patients with Hemodialysis-dependent End Stage Renal Disease (ESRD) during hemodialysis and on days off dialysis, and in patients with severe renal disease or ESRD not requiring dialysis. Defibrotide was not removed by hemodialysis, which had no notable effect on plasma clearance of defibrotide. Terminal half-lives were consistently less than 2 hours, and there was no accumulation of defibrotide following repeated dosing. Defibrotide exposure (AUC) in patients with severe renal impairment or ESRD was 50% to 60% higher than that observed in matched healthy subjects. Peak concentration (Cmax) was 35% to 37% higher following single- and multiple-dose administration of defibrotide.

- Thorough QT study or other QT assessment

  At a dose 2.4 times the maximum recommended dose, DEFITELIO does not prolong the QTc interval to any clinically relevant extent.

- Other notable issues: None

7. Clinical/Statistical- Efficacy

Clinical Review Team Recommendation: Approval
Statistical Review Team Recommendation: Approval

Source: Statistical Review

In this application, the applicant is seeking a full approval for defibrotide for the treatment of hepatic veno-occlusive disease (VOD) with (b) (4) dysfunction following hematopoietic stem-cell transplantation (HSCT).

The investigated product was submitted in NDA (b) (4) but based on issues identified by FDA including data collection and quality; the applicant withdrew the NDA in August 2011.

Study 2005-01 was submitted in the current application to support the proposed indication. The Study 2005-01 was a historical control, multicenter, open - label study to evaluate the efficacy and safety of defibrotide for the treatment of severe hepatic VOD in HSCT patients.

There were two cohorts in Study 2005-01. Defibrotide cohort enrolled 102 subjects, who took a fixed defibrotide dose of 25 mg/kg/day administered as 4 divided doses for a recommended minimum duration of 21 days. Historical control cohort had 32 subjects who received best supportive care. These 32 patients were selected from 6867 subjects undergoing HSCT at 35 medical centers, and reviewed by a Medical Review Committee (MRC) of the applicant (2 independent hematologists) in several rounds. The last round of selection was done after Data Safety Monitoring Board (DSMB) reviewed the interim efficacy results in defibrotide and historical control cohorts and suggested a re-selection of the historical control cohort. The primary efficacy endpoint was survival rate at day +100 post HSCT.

To adjust for the confounding effect from the potential prognostic factors, the propensity score adjusted analyses were performed using the quintiles/quartiles derived from the propensity score based on four pre-specified baseline prognostic factors. The two-sided 95.1% confidence interval of the treatment difference of survival rates adjusted for propensity score quintile/quartile was calculated, and when the lower bound exceeded 0, the applicant claimed the results as demonstrating superiority of the defibrotide cohort over the historical control cohort.

At day +100 post HSCT, there were 39 (38.2%) patients alive in the defibrotide cohort versus 8 (25.0%) patients in the historical control cohort, with an unadjusted estimated survival rate difference of 13.0% (95% CI [-4.6%, 31%]) and an adjusted estimated survival rate difference of 23.0% (95.1% CI [5.2%, 40.8%]) and a p-value of 0.011 from the propensity score adjusted analysis. The day +100 survival rates in subgroup analyses based on demographic characteristics appeared to support the primary results based on the sponsor's analyses. The defibrotide cohort also appeared to show improvement of the day +100 survival rate as compared with the historical control cohort based on time to event analyses.

However, due to the concerns of the validity of the propensity score adjusted analysis for small sample size and a variation of treatment effect estimates when varying propensity defined strata were used, the reviewer cannot confirm the sponsor's primary efficacy results for inference purposes (i.e. either the treatment effect estimates or the p-value). Nonetheless, the data show consistent numerical improvement of day +100 survival rate from the defibrotide treated cohort compared with the historical control cohort which may warrant further investigation.

In a dose finding study 99-118 (see Appendix for summary of the study), the day +100 survival rate was 44% for defibrotide treated arm at a dose of 25 mg/kg/day (95% CI: 32.5%, 55.9%). This result supports the day +100 survival rate estimated from Study 2005-01.

Source: Clinical Efficacy Review

The efficacy of defibrotide was evaluated by Day +100 survival after transplantation. This endpoint is the most meaningful endpoint for patients with severe VOD. Temporally, VOD occurs prior to Day +100 post-HSCT and most often occurs within the first 30 days post-HSCT.

Although survival at later dates (Day + 180) or overall survival represent a clinically meaningful outcome to patients. The temporal occurrence of VOD makes survival at Day +100 survival the endpoint that most accurately captures the efficacy of defibrotide.

Study 2005-01, demonstrated a Day +100 survival after transplantation in 25 patients [38% (95% CI: 29, 48)] in the defibrotide arm versus 8 patients [25% (95% CI: 12, 43)] in the historical control arm. The estimated difference in survival based on baseline prognostic factors demonstrated a clinically meaningful difference. The totality of evidence from the following three trials demonstrates a similar survival benefit for defibrotide in the treatment of hepatic VOD with end-organ dysfunction:

- Study 99-118: Survival at Day +100 post-HSCT was 44% (95% CI: 40,51) in the 25 mg/kg/day group.
- Study 2006: For the indication population (severe VOD with MOF post –HSCT) the Day +100 survival post-HSCT was 47% (95% CI: 42, 52).
- Study CIBMTR (Registry Data): The Day + 100 survival rate post-HSCT for the defibrotide group was 39% (95% CI: 24,56) versus 31% (95% CI: 19,45) for the non-defibrotide arm (best supportive care).

The studies demonstrated an analogous Day +100 survival rate post-HSCT, consistent with the treatment effect of defibrotide described in the historical control study 2005-01. The efficacy data from the single arm from Study 99-118 supports that defibrotide improves mortality at Day +100 after transplantation. The compassionate use treatment study (2006-05) also demonstrates an improvement in mortality for patients with hepatic VOD with end-organ dysfunction.

CDTL Comment: Multiple discussions occurred within the review team and involved discussions at the Office of Biostatistics and Office of Hematology and Oncology Products level. (b) (4) *efficacy labeling will be primarily descriptive, similar to the approach used for NDA 208159 Vistagard (uridine triacetate).* (b) (4) *In addition, efficacy claims will be limited to Day +100 survival results* (b) (4)

8. Safety

Source: Clinical Safety Review

Clinical Review Team Recommendation: Approval

The safety information was reviewed for 1894 individuals exposed to defibrotide in seven sponsored studies or trials of treatment of VOD, treatment of other disorders, prevention of VOD, or evaluations of PK and PD. One QT study was conducted in healthy volunteers. This safety information was supplemented by a retrospective registry study, available published

literature, legacy clinical study reports, and postmarketing information for all formulations of defibrotide. The doses of defibrotide in this summary are stated as defibrotide salt as identified in the individual protocols.

The types of safety data recorded (deaths, serious adverse events, adverse events of interest, common adverse events, adverse event characterization, common laboratory tests and vital signs) varied by protocol. None of the trials in patients with VOD collected all treatment-emergent adverse events. The best available adverse event information to assess safety of the proposed dose in the intended population was pooled data from 176 subjects with hepatic VOD and MOF after HSCT treated with defibrotide 6.25 mg/kg intravenously every 6 hours (total 25 mg/kg/day) in Studies 2005-01 and 99-118. This group is called the Selected Safety Population (SSP).

There were 105 males and 71 females with hepatic VOD and MOF after HSCT in the SSP. The median age was 25 years (range, 0.1-72 years). Pediatric patients comprised 37%, and there was a single subject ≥ 65 years old. Twenty-four percent of the subjects were ventilator- or dialysis-dependent. The subjects were treated with defibrotide for a median of 21 days (range, 1-83 days).

The results of ***analyses in the SSP pool*** showed:

- Mortality within 30 days of the last dose of defibrotide was 55%. The most common fatal adverse events were multi-organ failure (22%), respiratory failure (7%), pulmonary alveolar hemorrhage (4%), sepsis (4%), graft versus host disease (3%), renal failure (3%), pneumonia (2%), hepatic failure (2%) and hypoxia (2%). There were no deaths that could be clearly ascribed to defibrotide.
- The most common (≥10%) SAEs were multi-organ failure, hypotension, respiratory failure and renal failure (Table 68). The most common (≥1%) TEAEs resulting in treatment discontinuation were pulmonary alveolar hemorrhage, hypotension, multi-organ failure, catheter site hemorrhage, pulmonary hemorrhage, cerebral hemorrhage and sepsis (Table 69). SMQN Hemorrhage events resulted in discontinuation for 13% of the subjects.
- The most common (≥10%) TEAEs were hypotension, diarrhea, multi-organ failure, vomiting, renal failure, nausea, epistaxis, respiratory failure, hypertension, hypoxia and pyrexia (Table 70). The most common (>5%) grade 4-5 TEAE were multi-organ failure, respiratory failure, renal failure, hypotension, pulmonary alveolar hemorrhage and hypoxia.
- A grade ≥3 elevation was reported in 93% for bilirubin and in 27% for creatinine. In addition, 25% had a grade ≥3 elevation in aPTT, but the elevation of aPTT was not consistent over time with defibrotide use, and there was no dose-dependent increase in aPTT in Study 99-118.

In general, the analyses of the SSP revealed no unexpected events for patients with VOD after HSCT.

The clinically significant observations made by the applicant in ***comparative analyses*** included:

- In Study 2005-01, fatal hemorrhages were more frequent in the treatment group than in the historical controls (15% vs 6%), but the control group had a higher rate of fatal TEAE overall (section 8.4.1 of Clinical Review).
- The TEAE incidence was at least 5% higher in the treatment group than in the control group

for the TEAEs multi-organ failure, decubitus ulcer, catheter site hemorrhage, headache and pulmonary hemorrhage in Study 2005-01, and for respiratory failure during the prophylaxis phase of Study 2004 (Section 8.4.5.1 of Clinical Review).

- There were no important differences between study groups for changes in renal or hepatic function on Study 2005-01. In the prophylaxis phase of Study 2004, more subjects in the defibrotide arm has a shift to bilirubin >10 mg/mL than in the control arm, but a similar difference in shift to an extreme bilirubin was not observed in Study 2005-01. (Section 8.4.6.1 of Clinical Review)
- There was no adverse impact of defibrotide use on time to hematopoietic recovery or the incidence of graft failure in Study 2005-01 or in the prophylaxis phase of Study 2004 (Section 8.4.6.1 of Clinical Review).
- The outlier analysis of vital signs in Study 2005-01 showed no differences between the study groups for low systolic or low diastolic blood pressure (Section 8.4.6.2). (It should be noted that these vital sign measurements did not necessarily coincide with defibrotide infusion).
- In the QT study, no safety signal was identified on the basis of central tendency, outlier analysis, or exposure effect modeling (Section 8.4.6.3 of Clinical Review).

Overall, there were no substantial and consistent adverse effects of defibrotide when used as treatment or prevention of VOD in the HSCT recipients in comparison to safety outcomes in the respective control groups as assessed by the applicant. In support of a conclusion that defibrotide is safe, in two large (>1000 subjects) trials testing the efficacy of defibrotide 200 mg intravenously 4 times a day for thromboembolic prophylaxis after surgical procedures, the incidences of adverse reactions reported were low (<1% and 1.3%) (Section 8.9.2.3 of Clinical Review).

Hemorrhage is a clear potential adverse reaction for defibrotide based on its pharmacologic effects and the apparent dose-toxicity relationship (Section 8.4.5.2 of Clinical Review). In the SSP, events in the SMQN Hemorrhages (excluding laboratory terms) occurred in 59% of subjects, and the events were grade 4-5 for 20%. The most common Preferred Terms for hemorrhage were epistaxis (14%), gastrointestinal hemorrhage (9%), hematuria (9%), and pulmonary alveolar hemorrhage (9%). The Applicant noted that these event rates were comparable to those reported in the literature, and that by their analysis; hemorrhage events were less frequent on the defibrotide arm than on the control arm in Study 2005-01, suggesting that the proposed dose of 6.25 mg/kg every 6 hours is tolerable in this population. To ensure that safe use can be recapitulated in practice, the Prescribing Information should contain at least the same levels of controls as the protocols with regard to warnings, patient selection, monitoring, and treatment interruption for bleeding or invasive procedures.

Hypersensitivity is a second potential adverse reaction for defibrotide (Section 8.5.3 of Clinical Review). There were no immunogenicity studies performed. On analysis of clinical outcomes, events in the SMQN Hypersensitivity that were listed as related occurred in 1% of subjects in the SSP and <1% in Other Defibrotide-Treated Patients in the safety population. The majority of these events were types of rash, but further characterization was not possible due to the lack of narrative for these events. In three large (>1000 subjects treated with defibrotide) trials testing the efficacy of defibrotide (pre-1995 drug product) 200 mg intravenously 4 times a day or 400

mg intravenously twice daily for thromboembolic prophylaxis through 7 days after surgical procedures, the incidences of allergic reactions in the defibrotide-treated subjects were 0.5% to 0.8%. There was also one published case report of anaphylaxis after intravenous infusion of 200 mg of defibrotide, and hypersensitivity in this case was confirmed later by skin test. Although the incidence of hypersensitivity reactions is low, the occurrence of anaphylaxis warrants a warning in the Prescribing Information.

In the assessment of safety in ***special populations***, there was an inverse trend for pulmonary hemorrhage with age for the subjects in the VOD treatment trials, but this trend was not confirmed in the prophylaxis phase of the VOD prevention trial (Section 8.4.7.2 of Clinical review). There was an insufficient number of geriatric subjects in the safety database to allow for a meaningful analysis in this subgroup. There was a higher incidence of hemorrhage events and hypotension during defibrotide treatment in patients who were dialysis- or ventilator-dependent, but this could not be ascribed to defibrotide specifically, since the same trend was seen in the control group in Study 2005-01.

No formal ***drug-drug interaction*** studies were conducted by the applicant. Reports from the published literature showed that defibrotide enhanced the activity of dabigatran, UFH or LMWH ex vivo in human blood or plasma and in one clinical study in healthy volunteers (Section 8.7.5). The pharmacologic activity of defibrotide suggests that it might also be expected to enhance the activity of fibrinolytic agents. The increased risk of bleeding due to these effects of defibrotide contra-indicate concurrent use with anticoagulants and fibrinolytic therapies. In a murine model of induced thromboembolism, tranexamic acid counteracted the protective effect of defibrotide. Although this interaction is biologically plausible, there are no confirmatory clinical data.

There were no additional unexpected serious adverse events reported in the ***postmarket setting*** since the approval of defibrotide in Europe in 2013 for treatment of severe hepatic VOD following HSCT. The majority of the related serious adverse events reported were involved bleeding or coagulopathy. There were similarly few related unexpected serious adverse events recorded in the periodic safety updates for the years 1995-2008 for the other formulations of defibrotide marketed in Italy.

In summary, there was a high rate of adverse reactions in the patients being treated for hepatic VOD with MOF using the proposed dose-schedule of defibrotide, but there was no consistent signal that any of the events was caused specifically by defibrotide. The published reports of safety of defibrotide in other populations and the review of the postmarket reports are consistent with the relative tolerability of defibrotide in the VOD trials. Hemorrhage, hypersensitivity and pharmacologic interaction with anticoagulants and fibrinolytic therapies are safety concerns that can be mitigated by appropriate warnings, contra-indications and instructions for patient selection and dose modifications in the Prescribing Information. The lack of complete safety data from a well-conducted randomized trial is a substantial deficiency that raises questions about the accuracy of the safety profile in the intended population as currently established, and this residual concern needs to be considered when weighing the overall risks and clinical benefits of this therapy.

CDTL Comment: I concur with the safety assessment of the clinical reviewer.

9. Advisory Committee Meeting

There was no Advisory Committee meeting for Defitelio because the application did not raise significant public health questions regarding the role of Defitelio for this indication, and outside expertise was not necessary as there were no controversial issues that could benefit from an Advisory Committee discussion.

10. Pediatrics

Jazz Pharmaceuticals (formerly Gentium S.p.A) was granted orphan designation for defibrotide for the treatment of hepatic VOD on 21 May 2003.

The safety and effectiveness of Defitelio were established in pediatric patients based on results from Study 2005-01 and Study 99-118. The clinical trials enrolled 66 pediatric patients in the following age groups: 22 infants (1 month up to less than 2 years), 30 children (2 years up to less than 12 years), and 14 adolescents (12 years to less than 17 years). The efficacy and safety outcomes were consistent across pediatric and adult patients in both Study 2005-01 and Study 99-188.

Juvenile Animal Toxicity Data
A juvenile toxicity study in 21-day-old rats was conducted with intravenous bolus administration of defibrotide at 40, 150, or 320 mg/kg/day for 4 weeks. A delayed mean age of preputial separation was observed at all doses, suggesting a delay in onset of male puberty. The dose of 40 mg/kg/day is approximately 0.4 times the clinical dose on a mg/m2 basis for a child. The relevance of this finding for the onset of male puberty in humans is unknown.

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): No issues.
- Exclusivity or Patent Issues of Concern: No issues.
- Financial Disclosures: The Applicant adequately disclosed financial interests/arrangements with clinical investigators. The financial disclosure information did not raise questions about the integrity of the data. See Appendix 13.2 of the clinical review for details of the financial disclosure.
- Other GCP Issues: Data Quality and Integrity

In response to the comments identified by the Agency (b) (4)

(b) (4)

- Office of Scientific Investigation (OSI) Audits

  For full details, see the Clinical Inspection Summary by Dr. Orencia. Three clinical sites were selected and the rationale is provided below.

  The Applicant conducted Study 2005-01 at 35 sites with all but six sites in the US (Canada and Israel). There were a total of 102 patients in the treatment group and 32 patients in the final historical control group. The initial screening for the historical control group included over 6000 charts and was eventually narrowed down during the Medical Review Committee (MRC) selection process to 32 charts for review. These charts and data will not be available for site inspections and only the 102 treatment group patient's charts will be available for inspection.

Site inspections occurred at the three sites in the United States that enrolled the most patients into the treatment group arm of Study 2006-05. The three sites selected were chosen based on the total number of patients enrolled and critical and minor protocol violations. Critical protocol violations included the following: inclusion/exclusion criteria, informed consent documentation, concomitant medications and study drug deviations. The adherence to the inclusion and exclusion criteria in the treatment group is critical to ensure equipoise between the historical control group and treatment group. Minor protocol deviations include laboratory, daily weights and physical exam findings not recorded at proper time intervals or not completed at all. While these violations are termed minor these measurements are used to help determine complete remission of VOD as the secondary endpoint. A high degree of missing data may call into question the validity of the second endpoint and the study in general.

Site 01(Dana-Farber Cancer Institute) enrolled the largest number of patients (13) followed by Site 11(University of Minnesota Medical Center) (11) and lastly by site 08(Memorial Sloan Kettering) with 8 subjects. Site 11 and Site 08 had several critical protocol violations. Site 01 had fewer critical protocol violations but had numerous minor protocol violations to include laboratory and daily weights not performed on time.

Inspection of Jazz Pharmaceuticals, Inc. occurred from January 14 to 17, 2016. Monitoring deficiencies, in terms of initiating interim monitoring visits within a timely manner, were identified during the inspection. A Form FDA 483 was issued at the end of the sponsor inspection. Specifically, the sponsor monitoring activities for the clinical conduct of Study 2005-01 from 2006 until 2010 did not detect that some sites had lapsed IRB approvals. Inspectional review of ten sites for continuing IRB review found that five sites had lapsed approvals prior to the site being closed. One of the sites (Site #38 Nationwide Children's Hospital) had an actively enrolled subject during the time that IRB approval had lapsed.

The preliminary classification for Dr. Richardson and Dr. Kernan is No Action Indicated (NAI). The preliminary classification for Dr. Smith and Jazz Pharmaceuticals is Voluntary Action Indicated (VAI). Although regulatory violations were noted at the Dr. Smith and the sponsor site, the findings appear to be addressed in the NDA submission and unlikely to significantly impact overall assessment of efficacy for this study.

Clinical Reviewer Comment: The clinical review team discussed the findings of site 11 with Office of Scientific Investigations. All SAEs were eventually reported to the Agency and given frequent adaptations to the trial and iterative submissions of study protocol, delay in SAE reporting unlikely to impact overall assessment of efficacy for this study. The incorrect dosing calculations are not considered major violations and unlikely to impact overall assessment of efficacy for this study.

CDTL Reviewer Comment: I agree with the clinical review team assessment.

- Other outstanding regulatory issues: None

12. Labeling

The following are recommended major changes to the Defitelio prescribing information:

1. Indications and Usage
   - Modified indication to specifically state treatment of adult and pediatric patients.
2. Dosage and Administration
   - Clarified duration of treatment under Section 2.1.
   - (b) (4)
3. Warnings and Precautions
   - Recommended W&P: Hemorrhage and Hypersensitivity Reactions
   - (b) (4)
4. Adverse Reactions
   - (b) (4)
5. Clinical Studies
   - Descriptive approach will be used for efficacy findings, limited to Day +100 survival. (b) (4)

Labeling Consults

- Proprietary name: On 15 September 2015, OSE/DMEPA concluded that the proposed proprietary name, Defitelio, was found conditionally acceptable.

- Patient labeling/Medication guide: In general, Defitelio will be administered in an inpatient setting. A Medication Guide or Patient Package Insert is not needed for Defitelio.

- Carton and immediate container labels: DMEPA participated in the labeling discussions and provided recommendations for the container labels, carton and insert labeling. USAN nomenclature issue described in Section 3 will impact the carton and container labeling.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS): DRISK and the Division of Hematology Products (DHP) agree that based on the training and experience of the intended prescribers (e.g., hematologist and oncologists), and the site of administration will be in an inpatient setting, a REMS is not needed to ensure the benefits of defibrotide outweigh its risks.

Postmarketing Requirements (PMRs) and Commitments (PMCs): The Late Cycle Meeting Package sent to the Applicant on 13 January 2016 conveyed the following substantive review issues identified to date:

Clinical

1. The instructions for adverse event recording in the pivotal trial and the supporting studies excepted many events. As such, the safety profile for defibrotide in your proposed prescribing information (PI) may be incomplete. In order to confirm the verity of the proposed safety profile, you will need to submit safety results from a trial of defibrotide which required reporting of all adverse events.

2. The assessment of vital signs in the pivotal trial and the supporting studies was limited to daily measurement. This is not sufficient to objectively exclude the occurrence of infusion reactions. You will need to submit frequent measurements of vital signs during and immediately after infusion of defibrotide in a clinical study in order to assess objectively the incidence of infusion reactions.

3. You have provided no measurements of anti-drug antibodies in subjects treated with defibrotide.

In order to address the above issues, FDA recommended the following postmarketing requirements/commitments which were agreed to by the Applicant.

- Safety PMR #1: Conduct an analysis of safety in a randomized, open-label multi-center clinical trial comparing defibrotide versus best supportive care in the prevention of hepatic VOD in adult and pediatric patients, including all adverse events, laboratory abnormalities and frequent peri-infusion vital signs.

- PMC #1: Develop sensitive and specific anti-drug (defibrotide) binding and neutralizing assays. Submit validation reports on the assays in a final report to the NDA.

- PMC #2: Evaluate patients' sera for binding and neutralizing antibodies to defibrotide using the validated assays from PMC 1 and submit the data in a final immunogenicity study report.

Refer to action letter for final wording of the PMRs and PMCs.

CDTL Reviewer Comment: I concur with the above proposed PMR and PMCs.

14. Recommended Comments to the Applicant

None

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/s/

ROMEO A DE CLARO
03/03/2016