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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 208114
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 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)
Regulatory Action	*Approval*

Material Reviewed/Consulted	Reviewer
Division Director	Ann Farrell
Regulatory Project Manager	Beatrice Kallungal
CDTL	R. Angelo de Claro
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 known.

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 has a 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.

The risk-benefit profile was also discussed by Drs. Farrell, De Claro, Przepiorka and Wroblewski, all review team members recommend approval of this application, and I concur. This application will be given regular approval for the following indication: treatment of adult and pediatric patients with hepatic VOD, also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following HSCT.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

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Analysis of Condition	Toxic injury to hepatic endothelial cells from high dose chemotherapy can lead to hepatic VOD also known as SOS. The clinical symptoms include hepatomegaly, ascites, and weight gain. Most cases of hepatic VOD occur after 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).	Hepatic VOD is a rare condition that most often occurs after 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.
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 defibrotide 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 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 VOD, with renal or pulmonary dysfunction following HSCT. The results will be presented in a descriptive approach in the labeling (b) (4) . (b) ( )

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	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)	
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 AEs. In order to make the best safety assessment on AEs 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 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 AEs 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.	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 AEs 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 AE 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 SSP revealed no unexpected events for patients with VOD with multi-organ dysfunction after HSCT.

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	Study 2005-01 and 99-118 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 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 SAEs reported in the postmarketing setting since the approval of defibrotide sodium in Europe in 2013 for treatments of severe hepatic VOD following HSCT.	There were no substantial and consistent AEs 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 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 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.	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 provided by the Applicant.

2. Product Quality

There are no issues from a CMC perspective that would preclude approval.

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.

3. Nonclinical Pharmacology/Toxicology

There are no issues from a nonclinical perspective that would preclude approval.

The pharmacology and toxicology studies reviewed included those that assessed the pharmacodynamics, pharmacokinetics, genotoxicity, safety pharmacology, repeat dose toxicology 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.

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

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

Defitelio may cause fetal harm based on findings in animals. Exposure to defibrotide was associated with embryo-fetal toxicity in pregnant rabbits at doses approximately equivalent to the recommended clinical dose on a mg/m2 basis. 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.

4. Clinical Pharmacology

There are no issues from a clinical pharmacology perspective that would preclude approval.

Absorption, Distribution, Metabolism and Excretion (ADME)
After I.V. administration, peak plasma concentrations of defibrotide occur approximately at the end of each infusion. Defibrotide is highly bound to human plasma proteins (average 93%) and has a volume of distribution of 8.1 to 9.1 L. The precise pathway

of defibrotide degradation in plasma in vivo is largely unknown. 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.

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. 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.

- Intrinsic factors: 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 did not prolong the QTc interval to any clinically relevant extent.

5. Clinical Efficacy

The efficacy of defibrotide sodium was investigated in 528 patients treated on three studies: two prospective clinical trials and an expanded access study. The patients enrolled in all three studies had a diagnosis of hepatic VOD with multi-organ dysfunction after transplantation and received defibrotide sodium 6.25 mg/kg intravenously every 6 hours until resolution of VOD.

This approval was based on survival at Day +100 after HSCT. The Day +100 survival rates for Study 1, Study 2 and Study 3 were 38% (95% CI: 29%, 48%), 44% (95% CI: 33%, 55%) and 45% (95% CI: 40%, 51%) respectively. Based on published reports and analyses of patient-level data, the Day + 100 survival rates were 21% to 31% for patients with hepatic VOD with renal or pulmonary dysfunction who received supportive care or interventions other than defibrotide sodium. See Risk-Benefit Assessment for additional information.

6. Safety

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. Hemorrhage and hypersensitivity reactions are the major potential adverse reactions. The most common adverse reactions (incidence greater than or equal to 10%) were hypotension, diarrhea, vomiting, nausea, and epistaxis. In vitro defibrotide sodium has profibrinolytic activity. The use of defibrotide sodium is contra-indicated in patients being treated concurrently with anticoagulants or fibrinolytic therapies. See Risk-Benefit Assessment for additional information.

7. Advisory Committee Meeting

This application was not referred to ODAC for discussion because there were no controversial issues that could benefit from an Advisory Committee discussion.

8. Pediatrics

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

9. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not required.

- Other Postmarketing Requirements and Commitments

See action letter.

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/s/

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03/30/2016

RICHARD PAZDUR
03/30/2016