

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208114Orig1s000**

**SUMMARY REVIEW**

## Division Director Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Ann. T. Farrell, M.D., Division Director
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	208114
<b>Supplement #</b>	
<b>Applicant</b>	Jazz Pharmaceuticals
<b>Date of Submission</b>	July 31, 2015
<b>PDUFA Goal Date</b>	March 31, 2016
<b>Proprietary Name / Non-Proprietary Name</b>	DEFITELIO/defibrotide sodium
<b>Dosage Form(s) / Strength(s)</b>	Injection: 200 mg/2.5 mL (concentration of 80 mg/mL) single-use clear glass vial
<b>Applicant Proposed Indication(s)/Population(s)</b>	for the treatment of patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal [redacted] (b) (4) syndrome (SOS), with [redacted] (b) (4) [redacted] dysfunction following hematopoietic stem-cell transplantation
<b>Action/Recommended Action for NME:</b>	Approval
<b>Approved/Recommended Indication/Population(s) (if applicable)</b>	is indicated for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation (HSCT)

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	<b>Names of discipline reviewers</b>
Medical Officer Review	Tanya Wroblewski, M.D. /Donna Przepiorka, M.D.,

	Ph.D.
Project Manager	Beatrice Kallungal, BS
Associate Director for Labeling	Virginia Kwitkowski, RN, MS
Statistical Review	Cindy (Xin) Gao, Ph.D./Yuan-Li Shen, Dr. Ph./Rajeshwari Sridhara, Ph.D.
Pharmacology Toxicology Review	Brenda Gehrke, Ph.D./Ramadevi Gudi, Ph.D./ Christopher Sheth, Ph.D./Haleh Saber, Ph.D.
OPQ Review	Joseph Leginus/Nina Ni/Youmin Wang/Robert Wittorf/ Gerlie Gieser/Rabiya Laiq/Anamitro Banerjee/Raanan Bloom
Microbiology Review	Jessica Cole, Ph.D.
Clinical Pharmacology Review	Guoxiang Shen/Jee E Lee/Nitin Mehrotra, Ph.D./ Bahru A Habtemariam, Pharm.D./Brian P Booth, Ph.D.
OPDP	Nisha Patel, Pharm.D./Kathleen Davis
OSI	Anthony Orenca, M.D./Janice Pohlman, M.D., M.P.H./ Kassa Ayalew, M.D., M.P.H.
CDTL Review	Angelo DeClaro, M.D.
OSE/DEPI	none
OSE/DMEPA	Nicole Garrison, Pharm.D., BCPS/Michele Rutledge, Pharm.D./Yelena Maslov, Pharm. D./Lubna Merchant Pharm.D.
OSE/DRISK	Naomi Redd, Pharm.D./Cynthia LaCivita, Pharm.D.
Other	Moh Jee Ng/Jiang Liu/Qianyu Dang/Michael Li/Christine Garnett

OND=Office of New Drugs

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

# 1. Benefit-Risk Assessment

## Benefit-Risk Summary and Assessment

*Hepatic venous 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 (usually allogeneic). The mortality rate of hepatic VOD with multi-organ dysfunction is over 80% (Coppell et al. 2010). Currently no approved therapies exist for the recommended 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. A need exists for effective treatments. As a new molecular entity, defibrotide sodium demonstrates an improvement in Day 100 survival compared with historical controls for patients with hepatic veno-occlusive disease with renal and pulmonary dysfunction. The benefit-risk assessment supports regular approval for the recommended indication.*

*The efficacy of defibrotide sodium for the proposed indication was established based on the results of the following clinical trials: Study 2005-01 (prospective historical control trial), Study 99-118 (Phase 2 dose-finding trial), Study 2006-05 (expanded access protocol), and registry data from the Center for International Blood and Marrow Transplant Research (CIBMTR). The Day 100 survival rates in all four studies or clinical trials (range 38% to 45%) are greater than the historical control arm survival (25%), the supportive care arm from the CIBMTR registry study (31%), and published literature (< 20%). The consistent findings and totality of Day 100 survival findings across the trials/registry provide substantial evidence for the effectiveness of defibrotide sodium.*

*Defibrotide sodium appears to have a very 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 safety data from a randomized comparator trial. At the time of NDA submission, defibrotide sodium was already approved in the European Union and Israel. 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.*

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>Hepatic venous 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 (usually allogeneic). The mortality rate of hepatic VOD with multi-organ dysfunction is over 80% (Coppell et al. 2010).</li> </ul>	<p>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.</p>
<b>Current Treatment Options</b>	<ul style="list-style-type: none"> <li>There are currently no approved therapies for the recommended indication, and current standard of care consists of supportive therapy.</li> </ul>	<p>A need exists for effective treatment for patients with veno-occlusive disease.</p>
<b>Benefit</b>	<ul style="list-style-type: none"> <li>Defibrotide was studied in more than one single arms trial enrolling patients with hepatic VOD. These trials include the main study 2005-01, a supportive phase 2 dose-finding study 99-118, the expanded access trial 2006-05 and patient level data from a CIBMTR cohort who received defibrotide. The observed Day 100 survival in the trials where all enrolled patients had received defibrotide ranged from 38%- 45%.</li> <li>These observed Day 100 survival in the historical controlled data was 25%. The Day 100 survival data from the CIBMTR cohort who did not receive defibrotide was 31%. The reported Day 100 survival from the published literature in patients who did not defibrotide was less than 20%.</li> </ul>	<p>The trial results demonstrated a consistently greater frequency of Day 100 survival for those patients with hepatic VOD who received defibrotide compared with those patients with hepatic VOD who did not.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	<ul style="list-style-type: none"> <li>• The safety data included 1894 individuals exposed to defibrotide in seven sponsored studies or trials of treatment of VOD, treatment of other disorders, and prevention of VOD or evaluations of PK or PD.</li> <li>• The patient population in which this product was studied received multiple other drug products including antibiotics, products to prevent graft rejection, the transplant and stem cell product and mechanical ventilation and dialysis. The trials were mostly single arm and not randomized controlled trials. Therefore the safety characterization of defibrotide was very difficult.</li> <li>• The clinical safety reviewer conducted an analysis of pooled safety data 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 (expanded access protocol). This group is the Selected Safety Population (SSP) described in the primary review. No deaths could be clearly ascribed to defibrotide. The most commonly reported (<math>\geq 10\%</math>) SAEs in the SSP were multi-organ failure, hypotension, respiratory failure and renal failure. The most common (<math>\geq 1\%</math>) TEAES resulting in treatment discontinuation were pulmonary hemorrhage, cerebral hemorrhage and sepsis. The most common (<math>\geq 10\%</math>) TEAES in the SSP were hypotension, diarrhea, multi-organ failure, vomiting, renal failure, nausea, epistaxis, respiratory failure, hypertension, hypoxia and pyrexia. 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</li> </ul>	<p>Given the trials result especially when compared with the control data, there is no evidence that defibrotide increased the mortality using the Day 100 survival. Attribution of causality is extremely difficult in a patient population receiving multiple other medications and undergoing other procedures. Defibrotide will be prescribed for a limited population in a bone marrow transplant unit where extensively trained physicians and nurses will oversee care. The adverse event profile can be described in labeling.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>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.</p>	
<p><b>Risk Management</b></p>	<p>Labeling – includes a complete description of the safety observed in the trials along with focused description in certain highlighted areas.</p>	<p>The Prescribing Information (PI) will include Information in the Contraindications, the Warnings and Precautions section. In particular, hemorrhage, hypersensitivity, and pharmacologic interaction with anticoagulants and fibrinolytic therapies are safety concerns that will be described and can be mitigated by appropriate warnings, contraindications and instructions for patient selection and dose modifications in the Prescribing Information. The US PI discussion of risks is similar to the label for the EU. A Post-Marketing Requirement (PMR) under FDAAA will provide additional clinical safety from a randomized controlled trial and provide data to update the label.</p>

<b>Dimension</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
		There will be PMRs to address immunogenicity which will also be used to update the label.

## 2. Background

On July 31, 2015 Jazz Pharmaceuticals submitted an NDA for defibrotide sodium, a new molecular entity.

From the clinical review:

*Defibrotide sodium (DEFITELIO) is a polydisperse mixture of predominately single-stranded polydeoxyribonucleotide sodium salts derived from porcine intestinal tissue. Defibrotide sodium demonstrates profibrinolytic properties in vitro but the exact mechanism of action is not fully understood. The recommended indication for defibrotide sodium is for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD) [also known as sinusoidal (b) (4) syndrome (SOS)] with (b) (4) renal or pulmonary dysfunction. Defibrotide sodium is a new molecular entity (NME). The recommended dosing regimen for defibrotide sodium is 6.25 mg every 6 hours for a minimum of 21 days or until resolution of veno-occlusive disease.*

This application was given priority review. No treatments are approved for the treatment of veno-occlusive disease in the United States.

Defibrotide sodium is approved in the European Union and Israel at this time.

## 3. Product Quality

No issues were identified that would preclude approval.

From the review:

*Defibrotide is a polydispersion of the sodium salt of predominantly single-stranded oligodeoxyribonucleotides produced from a pool of mucosa extracted from intestines of healthy pigs. It is formulated in the drug product as a sterile aqueous solution at a concentration of 80 mg/mL for intravenous administration for severe hepatic venoocclusive disease in hematopoietic stem cell transplant patients. The product presentation is single-use vials containing (b) (4) mg and (b) (4) mg lyophilized powder.*

From the review:

*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 the excursions permitted to 15 – 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, and thus granted.*

I concur with the recommendation for approval. Issues regarding binding and neutralizing issues will be addressed as post-approval commitments. Draft language can be found in Section 13 of this review.

#### **4. Nonclinical Pharmacology/Toxicology**

No issues that would preclude approval were identified. From the secondary review:

*Defibrotide is a sodium salt of a complex of mainly single-stranded polydeoxyribonucleotides derived from porcine intestinal tissue, being developed as a treatment for hepatic VOD with evidence of multi-organ dysfunction following HSCT. The drug will be formulated into a sterile aqueous solution for intravenous administration. Defitelio is to be administered at a dose of 6.25 mg/kg by a 2-hour intravenous infusion every 6 hours (total daily dose of 25 mg/kg/day) for a minimum of 21 days.*

*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.*

*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/m<sup>2</sup> 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.*

*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 (b) (4)*

*The nonclinical studies needed to support product labeling were reviewed by Drs. Brenda Gehrke and Ramadevi Gudi. The nonclinical findings are summarized in the "Executive Summary" of the NDA review and reflected in the product label.*

I concur with the recommendation for approval.

## **5. Clinical Pharmacology**

No issues that would preclude approval were identified. The following text is from the primary review:

*The Phase 2 data showed that the 25 mg/kg/day dose provided a favorable benefit-risk profile. The Phase 3 trial was thus conducted using defibrotide dose of 25 mg/kg/day and the comparator group was a historical control (HC) receiving best supportive care.*

*In the pivotal study 2005-01, primary efficacy endpoint of Day+100 survival rate was 38.2% in defibrotide group and 25.0% in the HC group. All grades TEAEs considered to be possibly related to defibrotide including hemorrhage and hypotension did not occur at a higher incidence in the defibrotide group compared to historical controls.*

*Results from a legacy study IRI-151612 in healthy volunteers using intravenous 125I-Defibrotide suggested that urinary and fecal excretions accounted for 71% and 19% of the administered drug, respectively, with 10 to 14% of the administered drug excreted in the urine as parent drug. In subjects with end stage renal disease (ESRD), urinary excretion of the parent drug decreased to 5%. Overall, the data suggest that defibrotide is mainly eliminated by metabolism followed by renal excretion, and only a small portion of defibrotide is eliminated unchanged by the kidney.*

*The Phase 2 and the Phase 3 trials enrolled VOD patients with multi-organ dysfunction, including those with renal and hepatic impairments, since organ impairment is the natural history of VOD. Therefore, since the proposed dosing regimen was evaluated in the presence of hepatic and renal impairment, dose-adjustment is not recommended in these populations.*

Furthermore, 48.3% of those treated with defibrotide dose of 25 mg/kg/day in both trials were pediatric patients  $\leq$  16 years (48.6% of them aged 2-11 years), which is supportive of the proposed dose of 25 mg/kg/day for children.

Literature and in vitro study data suggest that defibrotide is predominantly degraded by exonucleases in human plasma then by various enzymes involved in DNA degradation.

Defibrotide is not a substrate, inhibitor, or inducer of any of the known drug metabolizing enzymes or transporters.

I concur with the Clinical Pharmacology review.

## **6. Clinical Microbiology**

Not applicable

## **7. Clinical/Statistical-Efficacy**

From the primary clinical review:

*The effectiveness of defibrotide sodium is based on efficacy results from the following studies: Study 2005-01 (prospective, historical control study), Study 99-118 (dose-finding study), Study 2006-05 (an expanded access clinical study), and subject level data from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry (Study CIBMTR).*

*The prospective historically controlled trial (Study 2005-01) enrolled 102 patients in the defibrotide arm and 32 historical controls. All patients had a diagnosis of hepatic VOD with renal or pulmonary dysfunction. Efficacy results in Study 2005-01 evaluated by Day+100 survival after transplantation demonstrated an observed survival rate of 38% (95% CI: 29, 48) in the defibrotide arm compared to 25% (95% CI: 12, 43)] in the historical control arm. In the phase 2 dose finding study (Study 99-118), 75 patients with VOD and multi-organ dysfunction who received the recommended defibrotide sodium dose demonstrated a Day + 100 survival of 44% (95% CI: 33, 55). In the expanded access study (Study 2006-05), 351 patients with VOD with multi-organ dysfunction who received the recommended dose of defibrotide sodium showed a Day+100 post-HSCT survival of 45% (95% CI: 40,51). The CIBMTR registry study evaluated 41 subjects with VOD with multiorgan dysfunction at the recommended dose of defibrotide sodium and 55 patients with VOD with multi-organ dysfunction that received standard of care (supportive therapy). The Day+100 survival post-HSCT in the defibrotide sodium arm was 39% (95% CI: 24, 56) compared to the standard of care arm of 31% (95% CI: 19-45).*

*The Day + 100 survival rates in all four studies are higher than the historical control arm survival (25%), the supportive care arm from the CIBMTR registry study(31%) and published literature (<20%). The totality and consistency of survival at Day + 100*

*after transplantation provides substantial evidence of efficacy for defibrotide sodium in patients with hepatic veno-occlusive disease with renal or pulmonary failure.*

I concur with the findings of the clinical review team (Drs. Wroblewski, Przepiorka, and DeClaro) regarding the evidence of effectiveness. Day 100 survival is an objective endpoint not subject to bias. This endpoint is appropriate because of competing risks of treatment-related mortality and relapse. Defibrotide use was consistently associated with a higher Day 100 survival rate than the Day 100 survival rate associated with lack of defibrotide use reported in the literature and the historical cohort control rate. Due to potential issues associated with the use of a historical control cohort, the Applicant engaged the services of the MRC to review the patient records for the inclusion and exclusion criteria of the patients to be enrolled in the historical cohort and the patients who were to be excluded. The Applicant's use of the MRC, an independent review group, strengthened their argument that the historical control group was a valid comparator.

I have read the statistical reviews and understand their statistical concerns regarding Study 2005-01: difficulty with accepting the propensity scores, concerns with the multiple revisions to the protocol and statistical analysis plan, the results from the sensitivity analyses, difficulty with determination of the significance level, and small sample size for the historical cohort. I agree that those are limitations of Study 2005-01. My recommendation for approval is not based on the results of Study 2005-01 alone; however, is based on all available data submitted by the Applicant as well as Agency literature reviews.

## **8. Safety**

The clinical reviewer conducted a thorough review and analysis of submitted safety data. Notable texts from the review include:

*Potential class safety issues might result from either the chemical class or the pharmacologic effect of a drug. Defibrotide is an oligonucleotide mixture. There are two FDA-approved oligonucleotides. Mipomersen (Kynamro) is a 20-mer oligonucleotide approved for treatment of homozygous familial hypercholesterolemia. It binds to and disrupts the function of apolipoprotein B mRNA. Labeling carries a warning about potential hepatotoxicity. It also causes flu-like symptoms and thrombocytopenia, and it is immunogenic. Pegaptanib (Macugen) is a 28-mer oligonucleotide conjugated to polyethyleneglycol (PEG) approved for treatment of neovascular age-related macular degeneration. It binds to and inhibits vascular endothelial growth factor. As it is administered by local injection, the majority of the adverse reactions to Pegaptanib are intraocular events, but labeling also carries a warning for anaphylaxis. The only unifying safety issues in this class are the potential for immunogenicity and hypersensitivity reactions.*

*Pharmacologically, defibrotide has been shown to enhance the enzymatic activity of plasmin to hydrolyze fibrin clots in vitro, and to increase t-PA and thrombomodulin expression while decreasing vWF and PAI-1 expression in microvascular endothelial cells in vitro. There are multiple FDA-approved thrombolytic drugs that enhance the activity of plasmin. These drugs carry warnings for bleeding, increased bleeding with concomitant use of anticoagulants or antiplatelet agents, and interference in coagulation tests in vitro. All of these can be considered expected safety issues for defibrotide based on its pharmacological effects...*

*There were no controlled trials that had adequate data for comparative analyses across all safety parameters for the intended population. Study 2005-01 was the only controlled trial in the intended population, but because the methodology used to collect adverse event (AE) data for the historical controls differed from that used in the treatment group (see Section 8.3.1 and 8.3.2), it was concluded that direct comparisons of treatment-related adverse events (TEAE) between these groups were not appropriate. Therefore, the objective of the safety review was to develop the safety profile descriptively for the intended population.*

Deaths within 30 days of the last dose of defibrotide were assessed. ..

*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%).*

Regarding Serious Adverse Events:

*The applicant reported that the most frequent (>3%) SAEs in subjects treated with defibrotide 25 mg/kg/day included multi-organ failure (22%), veno-occlusive liver disease (18%), hypotension (11%), respiratory failure (10%), renal failure 17 (10%), pulmonary alveolar hemorrhage (7%), sepsis (5%), hypoxia (4%), GVHD (4%), gastrointestinal hemorrhage (4%), pneumonia (3%), and pulmonary hemorrhage (3%) (Module 5.3.5.3 Integrated Summary of Safety Table 54).*

The FDA analyzed Treatment Emergent Adverse Events (TEAEs) resulting in discontinuation and noted (excluding VOD): pulmonary hemorrhage including alveolar, multi-organ failure, hypotension, catheter hemorrhage, cerebral hemorrhage and sepsis.

The FDA analysis noted the most frequent TEAEs were: hypotension, diarrhea, multi-organ failure, vomiting, renal failure, nausea, epistaxis and respiratory failure.

From the FDA Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review:

*No significant QTc prolongation effect of defibrotide intravenous solution (6.25 mg/kg and 15 mg/kg) was detected in this TQT study.*

I concur with the clinical reviewer regarding the safety data collection and assessments. Post-approval PMRs will be required of the Applicant to more fully characterize the safety and provide data on immunogenicity.

## 9. Advisory Committee Meeting

This application was not referred for an Advisory Committee meeting as no clinical efficacy or safety issues arose that required an Advisory Committee meeting and discussion.

## 10. Pediatrics

The Applicant submitted data from pediatric patients. The review team evaluated and recommended that the data be reported in labeling.

## 11. Other Relevant Regulatory Issues

The Office of Scientific Investigation (OSI) did not find the data unreliable in support of the application. The text from their review states:

*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.*

Financial Disclosure information was provided and reviewed. No issues arose during the review.

## 12. Labeling

All disciplines made recommendations for labeling.

The following comment from the clinical review team summarizes the major issues for the labeling.

*Reviewer Comment:* (b) (4)  
(b) (4)  
label. The (b) (4) was not included in the label (b) (4)  
(b) (4)

*The following text from the CDTL summarizes it as well:*

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)  
(b) (4)  
(b) (4)  
s not recommended.  
was not included in the labeling due to

In addition, efficacy claims will be limited to Day +100 survival results (b) (4)

Safety Information  
No boxed warning

Contraindications section lists concomitant administration of an anticoagulant or anti-fibrinolytic or hypersensitivity.

Warnings and Precautions subsections encompass:

Hemorrhage

Hypersensitivity

### 13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

None except for the labeling instructions and routine pharmacovigilance

- Other Postmarketing Requirements and Commitments

The issues for post-marketing requirements and commitments are for additional safety data and immunogenicity. Below are the original draft proposals:

PMR XXXX-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 veno-occlusive disease in adult and pediatric patients, including all adverse events, laboratory abnormalities and frequent peri-infusion vital signs.

PMC XXXX-2: Develop a sensitive and specific anti-drug (defibrotide) binding and neutralizing assay. Submit validation reports on the assay in a final report to the NDA.

PMC XXXX-3: Evaluate patients' sera for binding and neutralizing antibodies to defibrotide using the validated assays from PMC XXXX-2 and patient samples from a randomized, open-label multi-center clinical trial comparing defibrotide versus best supportive care in the prevention of hepatic veno-occlusive disease in adult and pediatric patients, and submit the data in a final immunogenicity study report.

Refer to action letter for final wording and milestones of the post-marketing requirements.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANN T FARRELL  
03/29/2016