CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208114Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management Review

Application Type	NDA
Application Number	208114
Submission #	S3-0002
OSE RCM #	2015 – 1659 (Master Record) 2015 – 1786 (Risk Management Plan)
Reviewer Name(s)	Naomi Redd, Pharm.D., Acting Team Leader
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	December 29, 2015
Subject	Review to determine if a REMS is necessary
Established Name	Defibrotide
(Proposed) Trade Name	Defitelio
Applicant	Jazz Pharmaceuticals
Therapeutic Class	Undetermined
Formulation(s)	IV infusion
Dosing Regimen	6.25mg/kg (max 25mg/kg/day) given as a 2 hour IV infusion for a minimum of 21 days.
Proposed Indication(s)	Treatment of patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), (b) (4) following hematopoietic stem-cell transplantation (HSCT).

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) defibrotide (Defitelio) is necessary to ensure the benefits of this product outweigh its risks. Jazz Pharmaceuticals submitted a New Drug Application (NDA) 208114 for defibrotide with the proposed indication for treatment of patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), (b) (4) following hematopoietic stem-cell transplantation (HSCT). Hemorrhage and the potential risk of embryo-fetal toxicity are risks associated with defibrotide. The applicant submitted a risk management plan in which they propose to mitigate any risks through labeling.

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.

1 Introduction

Jazz Pharmaceuticals submitted NDA 208114 for defibrotide with the proposed indication for the treatment of patients with VOD, also known as SOS, (b) (4) following HSCT. The applicant submitted a risk management plan in which they propose to mitigate any risks through labeling.

2 Background

2.1 PRODUCT INFORMATION

Defitelio (defibrotide), is a NME classified as a 505(b)(1) application, indicated for the treatment of patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), (b) (4) following hematopoietic stem-cell transplantation (HSCT). The recommended dose is 6.25mg/kg to be given every 6 hours as a 2 hour IV infusion for a minimum of 21 days. If signs and symptoms are present after 21 days, draft labeling as of December 21, 2015 recommends that treatment be continued until the symptoms are resolved.

Defibrotide is a sodium salt of polydeoxyribonucleotides derived from porcine intestinal tissue, with a half-life of approximately two hours. The pharmacological class and exact mechanism of defibrotide has not been fully elucidated; however, preclinical data of defibrotide performed on endothelial cells (ECs) in the human microvascular endothelial cell line suggest that this product is involved with several elements of the coagulation cascade. One of the key pathophysiological effects of VOD/SOS is the

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destruction of ECs, which can result in a prothrombotic-hypofibrinolytic state.[1] In vitro data for defibrotide appears to show mechanisms that reduce damage to ECs. These include increased tissue plasminogen activator (t-PA) and thrombomodulin expression and decreased von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1) expression, leading to reduced EC activation and increased EC-mediated fibrinolysis. Other in vitro data show that defibrotide protects ECs from damage caused by chemotherapy, tumor necrosis factor alpha (TNF- α), serum starvation and perfusion in addition to enhancing the enzymatic activity of plasmin to hydrolyze fibrin clots.[1]

Defibrotide was originally approved and marketed as Prociclide® and Noravid® in Italy in 1986 for the prophylaxis of deep vein thrombosis and treatment of thrombophlebitis. These indications were voluntarily withdrawn in 2009 to focus on the clinical development program for hepatic VOD.[2] The original manufacturer of defibrotide was Gentium S.p.A (formally Crinos- Villa Guardia [COMO]) based out of Italy and in January 2014, Gentium became a Jazz Pharmaceutical company. Europe granted marketing authorization in October 2013 for the treatment of severe hepatic VOD also known as SOS in HSCT therapy under the trade name Defitelio®, followed by approval in Israel May 2015 for the same indication under the same trade name. There is currently no approved therapy in the United States (US) for hepatic VOD/SOS, and defibrotide has only been available in the US through compassionate use programs since 1997.

The intended setting where defibrotide would be used is inpatient only, in those patients with VOD/SOS that exhibit multi-organ damage as a result of HSCT, and would be administered by hematologists and other healthcare providers who are versed and have access to treatment interventions for patients receiving chemotherapy and who may have complications from stem cell transplants.

2.2 REGULATORY HISTORY

The applicant was granted a rolling submission, with Priority review. The following is a summary of the regulatory history for NDA 208114 relevant to this review:

- 1997: The first US IND for defibrotide opened for VOD patients with multi-organ failure at Dana Farber Cancer Institute
- May 2003: Orphan Designation Granted
- December 2003: Gentium submitted IND 62118 to the US
- June 2011: Gentium submitted NDA 203230, but was later withdrawn in August 2011 due to issues related to the clinical data noted by FDA
- 12/11/2013: Preliminary comments for a Type B pre-NDA meeting in regards to the need for a REMS was given to the applicant: *"At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a*

[1] Defibrotide draft labeling, December 21, 2015

[2] Defibrotide module 2.5 Clinical Overview; Product Development Rationale page 7

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risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination regarding the need fora REMS during the review of your application."

- 11/3/2014: Request for submission of the application on a rolling review was granted
- 07/31/2015: Complete submission for NDA 208114 received for defibrotide
- 10/28/2015: Mid-cycle review meeting
- 11/13/2015: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data a REMS was not needed for defibrotide
- 03/31/2016: PDUFA Goal Date

(b) (4)

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Hematopoietic stem cell transplantation (HSCT) involves IV infusion of autologous or allogeneic stem cells collected from bone marrow, peripheral blood, or umbilical cord blood to reestablish hematopoietic function in patients with damaged bone marrow or a defective immune system. Each year, more than 50,000 first HSCTs, 28,000 autologous transplantation procedures, and 21,000 allogenic transplantations are performed worldwide, with annual increases of these procedures of 10-20%.[3]

Hepatic VOD/SOS is a rare and life threatening disease that occurs from EC damage and hepatocellular injury that result from high-dose chemotherapy that accompanies HSCT. These metabolites from chemotherapy cause the release of cytokines that induce activation of hepatocellular endothelial cell adhesion and detachment, followed by activation of the coagulation pathway which leads to severe hepatocyte damage. Clinical features of VOD/SOS include rapid weight gain (more than 5%), ascites, jaundice, painful hepatomegaly, and hypertension with multi-organ dysfunction often noted by pulmonary, renal, and cardiac failure. Incidence rates range from 8% to 14%, however some literature states that these rates can be as high as 40-60% depending on the presence of other clinical features. Symptoms of VOD/SOS have been reported as early as day 1 post-transplantation, but usually within 30 days, or later in the treatment course. In patients with mild disease, treatment is generally not required,

[3] http://emedicine.medscape.com/article/208954-overview#a2 accessed 12/21/15

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and if treatment is needed recovery is good. However, patients with mild disease can still progress rapidly due to concomitant underlying conditions and can experience symptoms that disrupt quality of life such as peripheral edema, renal insufficiency, and deficiencies in coagulation factors that lead to hemorrhagic events. Mortality rates from VOD/SOS can be higher than 80% within the first 100 days (Day+100) post-HSCT, and has been reported as a leading cause of death in this period.[4] In children, the mortality rate 100 days post transplantation is approximately 40%, as opposed to 9% in patients who do not have VOD/SOS.[5] Patients with this condition have poor quality of life and faster progression to death from disease complications. Prophylaxis or early therapy is essential to improve patient related outcomes and survival.

3.2 Description of Current Treatment Options

There are currently no drugs approved in the US to treat VOD/SOS. If approved, defibrotide would be the first drug used to treat this disease in the US. Management of VOD/SOS is currently limited to prophylaxis in those patients who are deemed high risk. These patients typically include those who are less than 1 year of age, have liver damage or prior liver transplantation, have an underlying infection or viruses, and/or impaired pulmonary, cardiac, or renal function. For patients already diagnosed with advanced VOD/SOS, supportive care with the use of diuretics, anticoagulants/antifibrinolytics, and dialysis are the only options for managing the symptoms of the disease.

4 Benefit Assessment[1]

The efficacy of defibrotide has been evaluated in several compassionate use studies in patients that range in ages 1 month to 72 years old. FDA evaluated two studies for efficacy (Studies 1 and 2), in addition to data from an expanded access program (Study 3) for further evaluation of safety.

***Study 1*:** This was an open-label multi-center, historical control study with 102 patients with a diagnosis of VOD treated with defibrotide, and 32 patients from a historical control group. The historical control group was obtained from review of patient records from 35 bone marrow transplant centers. This was done by an independent medical review committee blinded to patient outcomes. All patients had a diagnosis of hepatic VOD with multi-organ dysfunction upon study entry, and both groups were balanced for baseline prognostic factors for survival. The median age of the patients was 21 years old in the defibrotide group (1 month to 72 years old) and 18 years old in the historical control group (5 months to 57 years old). Defibrotide was administered at a dose of 6.25 mg/kg (max 25mg/kg/day) every 6 hours, with each dose infused over 2 hours, for a minimum of 21 days and continued until signs and symptoms of hepatic VOD resolved. The median duration of treatment was 22 days (range 1-60). The efficacy of defibrotide was evaluated at Day+100 post-HSCT; survival rates were 38% in the defibrotide treated arm, and 25% in the historical control arm.

[4] Dalle J et al. Hepatic Veno-Occlusive Disease after Hematopoietic Stem Cell Transplantation: Risk Factors and Stratification, Prophylaxis, and Treatment. *Biol Blood Marrow Transplant*. 24 September 2015; pg 1-10

[5] http://emedicine.medscape.com/article/989167-overview#a6 accessed 12/21/15

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***Study 2*:** This was a dose-finding study in 74 adult and pediatric patients that had a diagnosis of hepatic VOD and multi-organ dysfunction following HSCT treated with defibrotide at the recommended dose as above in Study 1. The median duration of treatment in this study was 19.5 days (range: 3-93 days), and survival rates at Day+100 was 44%.

Due to underlying co-morbid conditions, toxicities that can result from the disease itself, and limited clinical trial patient data, it is difficult to make a clear analysis on the true efficacy of defibrotide, though Day +100 survival rates appear to be supported in other studies evaluating defibrotide. Primary analysis shows an overall survival (OS) advantage at Day+100 with defibrotide treatment.[6] A secondary endpoint of complete response (CR) at Day+100 was higher in defibrotide treated patients versus historical control treated patients (26% versus 13% respectively). The sponsor has proposed a post marketing requirement/post marketing commitment (PMR/PMC) further evaluating the use of defibrotide (see section 7).

5 Risk Assessment & Safe Use Conditions[1,6]

The safety of defibrotide is based on an evaluation of approximately 900 patients exposed to defibrotide in the clinical development program, including 529 patients with hepatic VOD with evidence of multi-organ dysfunction following HSCT who received the recommended dose compared to 32 historical controls. The most common adverse reactions with an incidence of at least 1% or greater include hemorrhage, hypotension, diarrhea, nausea, and vomiting. Serious adverse reactions were reported for 13.2% of patients receiving defibrotide, and were hypotension (1.1%) and hemorrhage (pulmonary [3.4%], gastrointestinal [2.6%], and pulmonary alveolar [2.1%]). In Study 1, there were 35 patients (34.3%) who had at least 1 adverse reaction that permanently discontinued treatment. These reactions included: pulmonary alveolar hemorrhage (n=5), pulmonary hemorrhage (n=3), hypotension (n=3), catheter site hemorrhage (n=3), multi-organ failure (n=3), cerebral hemorrhage (n=2) and sepsis (n=2).

The table below includes non-hemorrhagic events and is based on 176 patients who received defibrotide at the recommended dose in Studies 1 and 2. In this patient population, 63% where greater than 16 years old, 59% where male and 78% were white. At study entry, 13% were dialysis dependent, 18% were ventilator dependent, and 89% had received an allogeneic HSCT. The reason for transplant in at least 43% of these patients was acute leukemia.

[6] Midcycle clinical meeting presentation slides.

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Table 1: Non-hemorrhagic Adverse Reactions in >10% of Patients treated with DEFITELIO 25 mg/kg/day (Studies 1 and 2) versus Historical Control (Study 1)[1]

Adverse Reactions, n (%)	DEFITELIO 25 mg/kg	Historical Control
Number of patients	**176**	**32**
Gastrointestinal disorders		
Diarrhea	43 (24.4)	12 (37.5)
Vomiting	31 (17.6)	8 (25.0)
Nausea	28 (15.9)	10 (31.3)
Vascular disorders		
Hypotension	65 (36.9)	16 (50.0)

5.1 HEMORRHAGE

Hemorrhagic events were evaluated separately event due to the risk of bleeding in this patient population, and all events with an incidence rate of more than 1% are noted in the table below. All grades, including fatal events, were noted in patients receiving defibrotide at the recommended dose in Studies 1 and 2. Severity data of these events were not collected in the historical control arm.

Additional hemorrhage events of any grade reported for the historical control arm and defibrotide arm, that did not meet the criteria for inclusion in table below include: conjunctival hemorrhage (9.4% and 6.3%), petechiae (28.1% and 5.1%), mouth hemorrhage (9.4% and 2.3%), ecchymosis (3.1% and 1.7%), bloody discharge (0 and 1.7%), hematoma (0 and 1.7%), vaginal hemorrhage (3.1% and 1.1%), and upper gastrointestinal hemorrhage (3.1% and 0.6%). The grade 3/4 events for just the defibrotide treated group included mouth hemorrhage (0.6%) and bloody discharge (0.6%).

Evaluation of hemorrhage was also done in the expanded access group (Study 3). Out of the 649 patients in this group, 201 (31%) reported hemorrhage of any grade. Pulmonary hemorrhage and gastrointestinal hemorrhage were the most commonly reported in 47 (7.2%) and 36 (5.5%) patients respectively.

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Table 2: Hemorrhagic Events: Historical Control (Study 1) and DEFITELIO 25 mg/kg/day Group (Studies 1 and 2) (≥1% of Grade 3 or 4 Adverse Reactions in DEFITELIO-Treated Patients)[1]

Adverse Reaction, n (%)	Historical Control (n=32)	DEFITELIO 25 mg/kg (n=176)		
	Any Grade [AEs Leading to Death]	Any Grade	Grade 3 or 4 AEs	AEs Leading to Death
With at least 1 AE of hemorrhage	**24 (75.0) [2 (6.3)]**	**101 (57.4)**	**51 (29.0)**	**16 (9.1)**
Pulmonary alveolar hemorrhage	5 (15.6) [2 (6.3)]	15 (8.5)	10 (5.7)	7 (4.0)
Cerebral hemorrhage	1 (3.1)	3 (1.7)	2 (1.1)	2 (1.1)
Pulmonary hemorrhage	0	7 (4.0)	3 (1.7)	2 (1.1)
Intracranial hemorrhage	0	5 (2.8)	3 (1.7)	2 (1.1)
Gastrointestinal hemorrhage	3 (9.4)	15 (8.5)	10 (5.7)	1 (0.6)
Hemorrhage	0	6 (3.4)	3 (1.7)	1 (0.6)
Epistaxis	5 (15.6)	24 (13.6)	6 (3.4)	0
Hematuria	5 (15.6)	15 (8.5)	4 (2.3)	0
Catheter site hemorrhage	0	10 (5.7)	4 (2.3)	0
Post-procedural hemorrhage	1 (3.1)	10 (5.7)	3 (1.7)	0
Hematemesis	3 (9.4)	9 (5.1)	4 (2.3)	0
Hemorrhagic cystitis	1 (3.1)	5 (2.8)	2 (1.1)	0
CNS hemorrhage	0	3 (1.7)	3 (1.7)	0

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5.1.1 Safe Use Conditions

Section 5.1 of Warnings and Precautions recommends that patients should be monitored for signs of bleeding and to give treatment or supportive care if warranted. The draft labeling also includes a table that gives specific recommendations on when to start and stop defibrotide in Section 2.2 of Treatment Modifications in the event of bleeding (Grade 1 or 2 and Grade 3 or 4) or surgical procedures. Concomitant administration with or administration (b) (4) of receiving anti-coagulant or anti-thrombotic therapy is contraindicated with defibrotide due to the increased risk of hemorrhage. In addition, there are also recommendations for patient counseling information to advise the patient to report any signs or symptoms of unusual bleeding, easy bruising, blood in urine or stool, headache, confusion, slurred speech, or altered vision, in addition to advising the patient to list all prescription medications, over the counter medications, or dietary supplements that may affect the risk of bleeding.

There are no other treatments approved at this time for VOD/SOS, therefore there are no other drugs to compare defibrotide to for the treatment of this condition. However, these recommendations are common with drugs used in this population of healthcare providers in this practice of medicine.

5.2 EMBRYO-FETAL TOXICITY

There are no available data with the use of defibrotide in pregnant women; however, administration of defibrotide to rats and rabbits during organogenesis resulted in embryo-fetal lethality.

5.2.1 Safe Use Conditions

The median age of patients treated with defibrotide was 21 years old. It is unclear if these patients were given contraceptive advice during the course of treatment. Recommendations in labeling are to advise females of reproductive potential to avoid pregnancy during treatment with defibrotide. These recommendations align with the high-dose chemotherapy that accompanies HSCT.

6 Expected Postmarket Use

Although defibrotide is not classified as a chemotherapeutic agent, the adverse reports reported at this time are similar to drugs that exhibit similar, if not the same adverse reactions commonly seen in this patient population. Defibrotide's intended use will be in inpatient settings where chemotherapy agents are commonly used by hematologists and other healthcare providers involved in oncology and hematopoietic stem cell transplantation that manage adverse events associated with these types of medications on a daily basis. At this time, the mechanism of action for defibrotide does not lend itself to be used in other conditions outside of hematologic events, nor is there the potential for abuse.

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7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for defibrotide beyond routine labeling. In an effort to obtain more data, the Applicant is proposing a PMR of a phase 3, randomized, open-label, multicenter study with an adaptive design comparing the efficacy of defibrotide versus BSC in the prevention of hepatic VOD in adult and pediatric patients. Negotiations of PMR's/PMC's were ongoing at the time of this review.

8 Discussion of Need for a REMS

In patients that receive HSCT, reductions in organ damage, infection, and severe, acute graft versus host disease (GVHD) contribute to improved outcomes. In a study of 854 patients who had survived at least 2 years after autologous HSCT for hematologic malignancy, 68.8% were still alive 10 years after transplantation.[3] Unfortunately; VOD/SOS is a severe and life-threatening complication that can result in patients who receive HSCT, and patient survival rates can be less than 20% within 100 days of post-HSCT.

The efficacy of defibrotide is based on data from historical controls and studies from compassion use programs. These data showed an OS advantage at Day 100, and survival rates of 38% to 44% at Day+100 of post-HSCT.

Common adverse reactions associated with defibrotide include hemorrhage, hypotension, and gastrointestinal effects. These reactions are often also a result of VOD/SOS or underlying co-morbid conditions, and are not unusual in this patient population. Recommendations for monitoring bleeding, including recommendations for treatment modifications, are outlined in labeling.

Non-clinical data did show that there was a risk of embryo-fetal lethality with the use of defibrotide. The median age of patients treated with defibrotide was 21 years old (range 1 month to 72 years), encompassing a wide age group that include females of reproductive potential. Recommendations in labeling are to advise women of reproductive potential to avoid pregnancy while taking defibrotide. In this patient population, exposure to other drugs with embryo-fetal or teratogenic effects for treatment of underlying malignancies is high. During HSCT patients will be exposed to multiple drugs that have the risk of embryo-fetal toxicity.

A REMS to communicate the risk of embryo-fetal or teratogenic effects or hemorrhage is not necessary in this patient population to ensure the benefits outweigh the risks of defibrotide. The benefit:risk evaluation is favorable for use in these patients to which there are limited treatment options. Supportive measures are the only available forms of therapy in patients with VOS/SOS. If approved, defibrotide would be the first US licensed product for treatment of this disease.

Defibrotide's likely prescribers will be hematologists and/or oncologists and the intended use will be in inpatient settings. Administration, monitoring and patient counseling will be done by hematologists and/or oncologists and other specialists that are familiar with the risks of hemorrhage and embryo-fetal toxicity in this patient population.

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9 Conclusion & Recommendations

Based on the available data, DRISK and DHP agree that the benefit-risk profile of defibrotide is acceptable and a REMS is not necessary to ensure the benefits outweigh the risks. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile.

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/s/

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12/29/2015

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