Formulary Drug Reviews

Defibrotide

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Each month, subscribers to *The Formulary Monograph Service* receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are available online to subscribers. Monographs can be customized to meet the needs of a facility. Through the cooperation of *The Formulary*, *Hospital Pharmacy* publishes selected reviews in this column. For more information about *The Formulary Monograph Service*, contact Wolters Kluwer customer service at 866-397-3433. The November 2016 monograph topics are apaziquone, crisaborole, irinotecan liposome, plecanatide, and telotristat. The Safety MUE is on methylnaltrexone PO.

Generic Name:	Defibrotide
Proprietary Name:	Defitelio (Jazz Pharmaceuticals)
Approval Rating:	1P
Therapeutic Class:	Hematological agents
Similar Drugs:	None
Sound or Look-Alike Names:	Deferasirox, Dofetilide, Definity, Enfuvirtide, Exenatide, Liraglutide, Nesiritide, Octreotide

INDICATIONS

Defibrotide is approved 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).¹

VOD is a rare and life-threatening disease that affects approximately 20% of patients who receive high-dose myeloablative conditioning therapy or HSCT.²⁻⁶ The disease is characterized clinically by increased serum bilirubin, hepatomegaly, fluid

retention, and weight gain.^{2,7} Its pathophysiology is of complex vascular origin consisting of hepatic venules and sinusoidal endothelial injury. The initial injury results in the deposition of platelet and coagulative material in the subendothelium, followed by subsequent fibrosis and occlusion of the terminal venous venules and sinusoids. Progressive venous occlusion and sinusoidal obstruction results in ischemia and structural damage of the acinus of the liver. VOD is implicated as one of the leading causes of HSCT-related morbidity and mortality.⁴

Typically, mild to moderate cases of VOD are self-limiting and resolve with minimal treatment; however, severe cases are associated with liver failure, hepatorenal syndrome, and multiorgan failure, with a mortality rate as high as 84%.^{2,3,6,8} Defibrotide is the only approved drug for the treatment of VOD with renal or pulmonary dysfunction following HSCT; however, patients may also be helped by supportive care, including diuresis, transfusion, renal replacement therapy, and analgesia.^{1,8} Experimental approaches to the prevention of VOD include administration of ursodeoxycholic acid, heparin, glutamine, antithrombin III, and prostaglandin E₁; however, these methodologies have shown limited efficacy.^{5,6,8,9} Patient-specific chemotherapy dosing

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regimens, reduced-intensity conditioning regimens, and the avoidance of cyclophosphamide are also methods used with some success to minimize the risk of developing VOD in patients undergoing HSCT.^{2,8}

Defibrotide is also being evaluated for prevention of VOD, prevention of acute graft-vs-host disease following allogeneic hematopoietic cell transplantation, treatment of VOD combined with antithrombin III or methylprednisolone, treatment of multiple myeloma, prophylaxis in sickle cell disease following myeloablative conditioning and haploidentical stem cell transplantation, treatment of patients with liver damage following peripheral stem cell transplantation, treatment of patients with severe peripheral ischemia (Fontaine stage IIb), and treatment of severe malaria.¹⁰⁻²¹

CLINICAL PHARMACOLOGY

Defibrotide is a polydisperse oligonucleotide prepared by controlled depolymerization of DNA obtained from porcine intestinal mucosa. It is the sodium salt of a single-stranded polydeoxyribonucleotide with a mean molecular weight of 15 to 30 kDa and affinity to adenosine receptors A₁ and A₂, resulting in thrombin antagonism.^{22,23}

Defibrotide has multiple and complex mechanisms of action, including anti-inflammatory, anti-atherosclerotic, anti-ischemic, and antithrombotic properties.^{1,4,7} Studies with defibrotide have also demonstrated increased plasmin activity, promotion of fibrinolysis via upregulation of tissue plasminogen activator and inhibition of tissue factor pathway, reduced circulating levels of plasminogen activator inhibitor-1, and increased concentration of endogenous prostaglandins (I₂ and E₂), which modulate thrombomodulin, platelets, and fibrinolysis.^{1,7,22,24}

Defibrotide may also be involved in the modulation of endothelial and leukocyte cellular interactions, which play a significant role in ischemic and reperfusion events due to alteration of endothelial cell membrane permeability, lipid peroxidation, free radical production, and recruitment of leukocyte adhesion to endothelial cells, resulting in vascular infiltration and subsequent endothelial damage.²⁵

The preferential binding of defibrotide to heparin-binding proteins, such as basic fibroblast growth factor and collagen I, is part of the mechanism responsible for the stimulation of the sinusoidal endothelium of the liver after a severe angiotoxic event. Promotion of endothelial cell mitogenesis and tubular morphogenesis results in the improvement of the clinical signs of VOD in patients following

a severe angiotoxic event.^{23,25} Additionally, defibrotide demonstrates the ability to prevent the signs of endothelial cell activation and damage by reducing intercellular cell adhesion molecule 1 expression and preventing activation of p38 and AKT pathways, resulting in protective anti-inflammatory and antithrombotic effects.^{26,27}

No clinically relevant changes in the QTc interval were observed at a dose of 2.4 times the maximum recommended dose.¹

PHARMACOKINETICS

Defibrotide demonstrates linear pharmacokinetics, with dose-dependent increases in volume of distribution, systemic exposure, and elimination occurring in healthy volunteers administered a single rapid intravenous (IV) infusion of defibrotide 0.5, 4, or 16 mg/kg. The mean volume of distribution following administration of defibrotide 0.5 mg/kg is 38.1 mL/kg, and for both the 4 and 16 mg/kg doses it is 54.6 mL/kg.²⁴ Defibrotide is highly bound to human plasma protein (93%) and has a volume of distribution of 8.1 to 9.1 L.¹ The mean systemic exposure (area under the curve [AUC]) following IV administration of 0.5, 4, and 16 mg/kg was 173, 1,385, and 8,178 mg/L/min, respectively. Administration of an IV infusion of defibrotide at 100 mg/h following a 200 mg bolus injection maintained plasma concentrations in the central compartment at 25 to 30 mg/L, with steady-state concentrations attained at 90 to 120 minutes.²⁴

Defibrotide is degraded into oligonucleotides, nucleotides, nucleosides, and then to the free 2'-deoxyribose sugar, purine, and pyrimidine bases.^{1,22,28} Plasma concentrations of defibrotide are maintained during continuous infusion and decrease rapidly following the end of infusion or rapid IV injection. Administration of low doses of defibrotide 0.5 and 4 mg/kg demonstrated a 1-compartment model of plasma elimination, characterized by a monoexponential equation. However, the pharmacokinetics of high-dose defibrotide (16 mg/kg) are best characterized with a 2-compartment open model of elimination, with a distribution and elimination phase characterized by a biexponential equation. The mean elimination half-life of defibrotide increases with dose, and the observed half-life following rapid IV administration ranges from 9.8 to 21.1 minutes.²⁴ The mean half-life after the recommended infusion rate and period is less than 2 hours.¹

With radiolabeled doses of defibrotide 6.25 to 12.5 mg/kg administered IV, 38% to 64% was eliminated in the urine and 24% to 26% in the feces.²² After a 2-hour infusion, 5% to 15% of the total dose was excreted in the urine as defibrotide, and the majority was excreted during the first 4 hours.¹ The pharmacokinetics of defibrotide do not appear to be altered by concurrent hemodialysis.^{1,8} Administration in patients with severe renal impairment or end-stage renal disease resulted in a 50% to 60% increase in the AUC and higher peak concentrations (35% to 37%).¹

COMPARATIVE EFFICACY

Indication: Treatment of Veno-Occlusive Disease in Stem Cell Transplant and Non-Stem Cell Transplant Patients

Guidelines

Guideline: British Committee for Standards in Haematology/British Society for Blood and Marrow Transplantation (BCSH/BSBMT) guideline: Diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation

Reference: Dignan FL, et al, 2013²⁹

Comments:

Prophylaxis: Defibrotide is recommended in adults and children to prevent VOD (SOS) following allogeneic stem cell transplantation in patients with the following risk factors: preexisting hepatic disease, second myeloablative transplant, allogeneic transplant for leukemia beyond second relapse, conditioning with busulfan-containing regimens, prior treatment with gemtuzumab ozogamicin, or diagnosis of primary hemophagocytic lymphohistiocytosis, adrenoleukodystrophy, or osteopetrosis. Ursodeoxycholic acid may also be used in the prophylaxis of VOD. Prostaglandin E₁, pentoxifylline, heparin, and antithrombin are not recommended.

Treatment: Defibrotide is recommended for the treatment of VOD (SOS) in adults and children. Tissue plasminogen activators are not recommended for treatment, and N-acetylcysteine is not routinely recommended. Methylprednisolone can be used, but the increased risk of infection needs to be considered.

Studies

Drug: Defibrotide

Reference: Chopra R, et al, 2000³⁰

Study Design: Retrospective, open-label, multicenter, European-based review of patients eligible for the compassionate use of defibrotide

Study Funding: Not specified

Patients: 40 patients with a clinical diagnosis of severe VOD following autologous or allogeneic stem cell transplantation.

Intervention: Patients received defibrotide 10 to 40 mg/kg/day in 4 divided doses infused over 2 hours. Based on patient-specific response to therapy or toxicity, appropriate adjustment of the initial dose was permitted. Median duration of treatment was 18 days (range, 2-71 days).

Results

Primary Endpoint(s)

- Complete response, defined as serum bilirubin less than 2 mg/dL and complete resolution of associated symptoms and signs of VOD, was observed in 55% (22 of 40) (95% confidence interval [CI], 40%-70%) of patients treated with defibrotide.
- Of 22 complete responders, 17 (77%) survived beyond 100 days posttransplantation.
- Younger patients had a better response with defibrotide therapy compared with older patients; the median age of responders was 18 years versus 41.5 years in nonresponders ($p = .001$).
- Complete response and survival beyond 100 days posttransplantation was observed in 36% (10 of 28) (95% CI, 21%-51%) of patients determined to be at poor risk, defined as a diagnosis of multiorgan failure or a greater than 40% probability of VOD progression at initial diagnosis.

Comments: Multiorgan failure was documented in 26 enrolled patients. A correlation between administered dose and response rate was not observed.

Reference: Corbacioglu S, et al, 2004³¹

Study Design: Retrospective, open-label, multicenter, European-based study

Study Funding: Not specified

Patients: 45 patients younger than 20 years with a clinical diagnosis of VOD following autologous or allogeneic stem cell transplantation and who had been treated with a variety of chemotherapy regimens. Medications intended for the prevention of VOD (eg, low-dose heparin, combination of heparin and ursodiol, combination of heparin and antithrombin III, combination of heparin and L-glutamine, ursodiol) were used by 80% of patients. The median day of VOD diagnosis was 12 days posttransplant (range, 0-58 days).

Intervention: Median dosage was defibrotide 40 mg/kg/day (range, 10-110 mg/kg/day) infused over a 2- to 4-hour period for a median duration of 17 days (range, 1-83 days). The median delay to

start of defibrotide therapy was 1 day after diagnosis (range, 0-12 days). Previous medications for the prevention of VOD were not discontinued.

Results

Primary Endpoint(s)

- Complete response, defined as resolution of VOD and multiorgan failure plus a decrease in bilirubin to less than 2 mg/dL, was observed in 76% (34 of 45) of patients.
- Posttransplantation survival beyond 100 days was observed in 64% (29 of 45) of patients.
- Complete response rate in patients treated only with defibrotide was 75% (18 of 24) versus 76% (16 of 21) in patients who received additional treatment.
- The median age of complete responders was not different from nonresponders.
- The average delay from diagnosis of VOD to start of treatment with defibrotide was 1 day in the complete response group and 5.5 days in the nonresponder group ($p < .01$). These values were 1.3 and 5.5 days ($p < .01$), respectively, in patients with severe disease.

Comments: Prophylactic use of low-dose heparin or the use of additional treatment modalities consisting of antithrombin III, low-molecular-weight heparin, prostaglandin E₂, tissue plasminogen activator, protein C concentrate, and C1 esterase inhibitor was observed.

Drug: Defibrotide vs Historical Control

Reference: Richardson P, et al, 2016^{32,33}

Study Design: Nonrandomized, historical control, open-label, multicenter phase 3 study

Study Funding: Gentium S.p.A. (Jazz Pharmaceuticals)

Patients: 102 patients with a clinical diagnosis of VOD by day 21 posttransplantation and with renal and/or pulmonary failure by day 28 posttransplantation, and 32 historical control patients who met the criteria for diagnosis of VOD with multiorgan failure.

Intervention: Patients received defibrotide 25 mg/kg/day administered in 4 divided doses (6.25 mg/kg every 6 hours) infused over a 2-hour period for a minimum of 21 days and were compared with historical control patients. Median duration of defibrotide therapy was 21.5 days (range, 1-58 days).

Results

Primary Endpoint(s)

- Survival rate at day 100 post-HSCT was 38.2% in the defibrotide group and 25% in the historical control group; absolute treatment difference

was 13.2% (95% CI, 5.2%-40.8%; $p = .011$), and the number needed to treat (NNT) for this group was 8.

- Rate of complete response, defined as the resolution of multiorgan failure and decrease in bilirubin to less than 2 mg/dL, by day 100 posttransplantation was 25.5% in the defibrotide treatment group versus 12.5% in the historical control group. Absolute treatment difference was 13% (95% CI, 3.5%-34.6%; $p = .016$), and the NNT for this group was 8.

Secondary Endpoint(s)

- Survival rate at day 180 post-HSCT was 32.4% in the defibrotide group and 25% in the historical control group, for a treatment difference of 16.4% (95% CI, -1.2% to 34.1%; $p = .067$).
- Complete response rate in children was 36% in the defibrotide treatment group versus 7% in the historical control group ($p = .04$).³²
- Survival rate at 100 days posttransplantation in ventilator-dependent patients was 9% versus 40% in patients who were not ventilator dependent ($p = .051$).³²
- Survival rate at 100 days posttransplantation in patients on dialysis was 34% versus 9% in patients who were not on dialysis ($p = .027$).³²
- Complete response rate in patients who received autologous stem cell transplantation was 75% in the defibrotide treatment group versus 0% in the historical control group ($p = .005$).³²

Comments: This study was conducted at 35 centers in the United States, Canada, and Israel.

Limitations: The size of the historical control group was small, so selective bias may have occurred. Direct comparative studies with other therapies or placebo are not possible because of the size of the patient population with this medical condition. This study was not powered for any of the secondary outcomes.

Reference: Richardson RG, et al, 2011^{34,35}

Study Design: Prospective, open-label, multicenter study; updated results of a treatment investigational new drug (IND) expanded access protocol

Study Funding: Gentium S.p.A.

Patients: At interim analysis, 269 patients with a diagnosis of VOD and multiorgan failure following stem cell transplantation or chemotherapy were enrolled.

Intervention: Patients received defibrotide 25 mg/kg/day administered in 4 divided doses for a minimum of 21 days. Mean duration of defibrotide treatment was 22 days (range, 1-88 days).

Results

Primary Endpoint(s)

- Rate of complete response, defined as a decrease in bilirubin to less than 2 mg/dL and resolution of multiorgan failure, at 100 days after transplantation or initiation of chemotherapy was achieved in 32% (85 of 269) of patients, with a survival rate beyond 100 days of 50% (estimate by Kaplan-Meier).
- Complete response rate in the 134 patients who met the original enrollment criteria was 30% versus 9% in the historical control group ($p < .001$), and the survival rate beyond day 100 was 46% versus 25%, respectively ($p = .006$).

Comments: This study is referred to as “study 3” in the defibrotide prescribing information. A total of 351 patients were included in the analysis. The median duration of treatment was 21 days. Survival at day 100 post-HSCT was 45% (95% CI, 40%-51%).¹

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Coadministration of defibrotide with systemic anticoagulant or fibrinolytic therapy is contraindicated. Defibrotide is also contraindicated in patients with known hypersensitivity to defibrotide or any of its excipients (sodium citrate, water for injection, hydrochloric acid, and sodium hydroxide).¹

Warnings and Precautions

Defibrotide should not be initiated in patients with active bleeding. The drug increases the activity of fibrinolytic enzymes and may increase the risk of bleeding in patients with VOD after HSCT. If bleeding occurs, therapy should be discontinued, the underlying cause treated, and supportive care provided until the bleeding has stopped.¹

Concomitant use of defibrotide and a systemic anticoagulant or fibrinolytic therapy (except for routine maintenance or reopening of central venous lines) may increase the risk of bleeding. Discontinue anticoagulants and fibrinolytic agents prior to initiating defibrotide treatment, and consider delaying the start of defibrotide administration until the effects of the systemic anticoagulant have abated.¹

Hypersensitivity reactions to defibrotide (eg, rash, urticaria, angioedema, anaphylaxis) have been reported (less than 2% incidence).¹

The efficacy and safety of defibrotide during pregnancy in humans are unknown. Animal models

have indicated a potential risk for decreased implantation and miscarriage.¹

Safety of defibrotide in breast-feeding has not been established. There is no information regarding the presence of defibrotide in human milk or the effects on milk production or the breast-fed infant. Breast-feeding is not recommended because there is a potential for bleeding in the breast-fed infant.¹

The safety and efficacy of defibrotide in pediatric patients have been established in a small number of patients ($n = 66$) enrolled in clinical trials. Safety and efficacy outcomes were consistent across pediatric and adult patients in defibrotide trials.¹ Further pediatric assessment is not required by the US Food and Drug Administration (FDA) because defibrotide is classified as an orphan drug.³⁶

ADVERSE REACTIONS

Treatment with defibrotide is generally well tolerated. In clinical trials, the most common adverse reactions were hypotension (37%), diarrhea (24%), vomiting (18%), nausea (16%), and epistaxis (14%). The most common serious adverse reactions (incidence of 5% or greater) were hypotension (11%) and pulmonary alveolar hemorrhage (7%). Hemorrhage events of any type and any grade occurred in 59% of patients, and these events were grade 4 to 5 in 20% of patients. Adverse reactions that led to permanent discontinuation of defibrotide therapy included pulmonary alveolar hemorrhage, pulmonary hemorrhage, hypotension, catheter-site hemorrhage, multiorgan failure, cerebral hemorrhage, and sepsis.¹ Adverse reactions reported for the 710 patients treated in the International Compassionate Use Program were similar to those reported in clinical trials.³⁷

DRUG INTERACTIONS

Increased risk of bleeding may occur with concomitant use of antithrombotic (eg, heparin) or fibrinolytic drugs (eg, alteplase). Concomitant use of defibrotide with these types of drugs is contraindicated.¹

Defibrotide does not induce cytochrome P450 (CYP-450) 1A2, 2B6, 3A4, or UGT1A1 or inhibit CYP1A2, 2B6, 3A4, 2C8, 2C9, 2C19, 2D6, UGT1A1, or UGT2B7, and is not a substrate or inhibitor of the uptake transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, and OATP1B3 or the efflux transporters P-glycoprotein and breast cancer resistance protein. Therefore, pharmacokinetic drug-drug interactions are unlikely.¹

RECOMMENDED MONITORING

Monitoring may include clinical markers of VOD resolution or progression. Specific monitoring related to drug-induced toxicity should focus on bleeding-related events and hypersensitivity reactions.

DOSING

The recommended dosage of defibrotide for adult and pediatric patients is 6.25 mg/kg every 6 hours given as a 2-hour IV infusion. The dose should be based on patient baseline body weight, defined as patient weight prior to the preparative regimen for HSCT. Administer defibrotide for a minimum of 21 days; if after 21 days the signs and symptoms of hepatic VOD have not resolved, the drug can be continued until resolution of VOD or up to a maximum of 60 days of therapy.¹ A few patients have been treated with doses ranging from 60 to 110 mg/kg/day; however, studies have shown no improvement in survival with doses above 40 mg/kg/day.^{8,38} Increased toxicity (eg, bleeding) was not observed until the dose was higher than 100 mg/kg/day.³⁸

The defibrotide solution must be diluted prior to IV administration. The total dose should be constantly infused over a 2-hour period, using an infusion set equipped with a 0.2 micron in-line filter. Coadministration with other drugs in the same IV line is not recommended.¹ The IV administration line should be flushed with dextrose 5% injection or sodium chloride 0.9% injection before and after administration.¹

A visual compatibility evaluation of defibrotide with select drugs during simulated Y-site administration found 7 drug solutions (amikacin, furosemide, midazolam, mycophenolate mofetil, nicardipine, tobramycin, and vancomycin) that were visually incompatible with defibrotide solution; coadministration with

these drugs should be avoided. Another 36 drugs were visually compatible with the defibrotide solution over a 4-hour observation period.³⁹

Modification of the dosing regimen may be required because of hypersensitivity reactions, bleeding, or invasive procedures (see Table 1).¹

PRODUCT AVAILABILITY

In July 2011, the FDA accepted the New Drug Application (NDA) for the use of defibrotide in the treatment of VOD in children and adults undergoing HSCT. The FDA also granted defibrotide orphan drug and fast track designations in order to facilitate development and expedite review.⁴⁰ However, the NDA was voluntarily withdrawn by Gentium in 2011 because of concerns raised by the FDA regarding completeness of the datasets for the treatment and prevention studies.⁴¹ Defibrotide sodium was approved by the FDA on March 30, 2016.³⁶

Defibrotide sodium is available as a 200 mg per 2.5 mL preservative-free solution in glass vials. Each vial is intended for a single patient, and any partial vials should be discarded.^{1,36} The diluted defibrotide solution should be used within 4 hours if stored at room temperature or within 24 hours if refrigerated. Up to 4 doses of defibrotide solution may be prepared at one time if refrigerated.¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for defibrotide.³⁶

CONCLUSION

The incidence of mortality in severe VOD following stem cell transplantation remains high. Given the lack of currently viable treatment options for VOD, as well

Table 1. Modification to defibrotide dosing regimen because of toxicity or invasive procedures¹

Event	Recommended modification or action
Severe or life-threatening hypersensitivity reaction (anaphylaxis)	Discontinue defibrotide permanently; do not resume treatment.
Persistent, severe, or potentially life-threatening bleeding	Withhold defibrotide; treat the cause of bleeding and give supportive care as needed, then consider resuming treatment (at the same dose and infusion volume) once bleeding has stopped and the patient is hemodynamically stable.
Recurrent significant bleeding	Discontinue defibrotide permanently; do not resume treatment.
Invasive procedures	There is no known reversal agent for the profibrinolytic effects of defibrotide. Discontinue defibrotide infusion at least 2 hours prior to an invasive procedure. Resume defibrotide treatment after the procedure, as soon as any procedure-related risk of bleeding is resolved.

as the limited nature of supportive care, defibrotide represents a promising therapy for VOD. In a pivotal phase 3 historical control trial, the 100-day complete response rate was higher in the defibrotide treatment group compared with the historical control group (25.5% vs 12.5%, respectively).

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