DEFITELIO®
(defibrotide sodium) injection 80 mg/mL

THE PATHOPHYSIOLOGY OF VOD AND THE MECHANISM OF ACTION OF DEFITELIO[a]

The first and only approved treatment for veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS)

Indication

Defitelio® (defibrotide sodium) 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).

IMPORTANT SAFETY INFORMATION

Contraindications

Defitelio is contraindicated in the following conditions:

- Concomitant administration with systemic anticoagulant or fibrinolytic therapy
- Known hypersensitivity to Defitelio or to any of its excipients

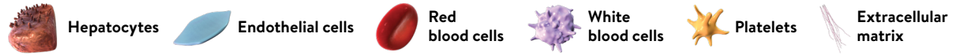
Please see additional Important Safety Information on back and accompanying full Prescribing Information.

[a]Based on preclinical studies

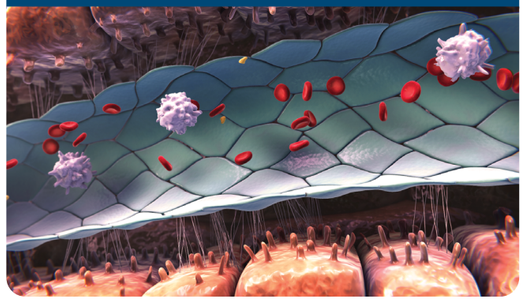
Progressive cascade of VOD

VOD and the sinusoidal endothelium

Based on experimental models, buildup of toxic metabolites from HSCT conditioning regimens may trigger damage to hepatocytes and activation of and damage to sinusoidal endothelial cells in the liver. This can lead to a cascade of events that is potentially life-threatening.[1-3]



HEALTHY SINUSOID



Sinusoidal endothelial cells provide a barrier between the blood and hepatocytes and regulate hemostasis, permeability, vascular tone, and immune and inflammatory responses.[4]

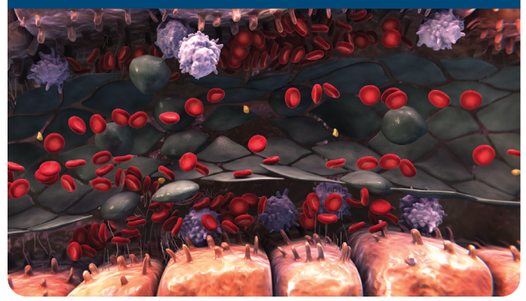
ENDOTHELIAL DAMAGE

Activation of endothelial cells triggers expression of cytokines and adhesion molecules, activating inflammatory pathways that cause additional endothelial damage.[1-3]

In addition, release of the enzyme heparanase contributes to degradation of the extracellular matrix, loss of cytoskeletal structure, and gap formation between sinusoidal endothelial cells.[1-3]

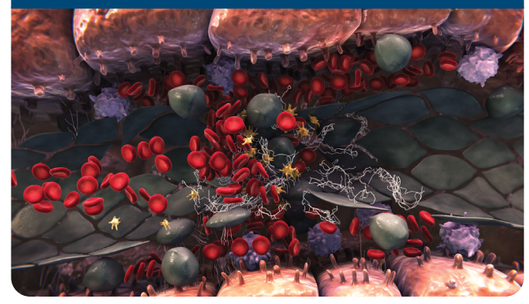
Degradation of the extracellular matrix leads to detachment of endothelial cells from the sinusoidal lining.[4,5]

SINUSOIDAL NARROWING



This ongoing degradation of the endothelium allows red blood cells, leukocytes, and cellular debris to move into the space of Disse. This can lead to sinusoidal narrowing, which may lead to endothelial cells embolizing downstream and contribute to sinusoidal blockage.[1,2]

SINUSOIDAL BLOCKAGE



Sinusoidal endothelial cell damage also triggers the expression of multiple factors that regulate coagulation and fibrinolysis (table A).[2,6,7]

All of these events can lead to a procoagulant and hypofibrinolytic state, where fibrin deposition, clot formation, and sinusoidal narrowing can cause further blockage.[1,2,8]

Hepatocyte cell death is a consequence of sinusoidal disruption, and further sinusoidal obstruction may lead to a reduction in hepatic venous outflow and to post-sinusoidal hypertension.[1-4]

This cascade of cellular events appears to occur before clinical and laboratory manifestations are present[1,2]

A. FACTORS THAT REGULATE COAGULATION AND FIBRINOLYSIS[2,6,7]

Factor	Function
von Willebrand factor	stimulates platelet aggregation
Tissue factor	promotes activation of factor X
Plasminogen activator inhibitor-1	reduces fibrinolysis

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hemorrhage—Defitelio may increase the risk of bleeding in patients with VOD after HSCT. Do not initiate Defitelio in patients with active bleeding. Monitor patients on Defitelio for signs of bleeding. If bleeding occurs, withhold or discontinue Defitelio.

Concomitant systemic anticoagulant or fibrinolytic therapy may increase the risk of bleeding and should be discontinued prior to Defitelio treatment. Consider delaying Defitelio administration until the effects of the anticoagulant have abated.

Please see additional Important Safety Information on back and accompanying full Prescribing Information.

Clinical manifestations and progression of VOD

Sinusoidal obstruction may lead to a reduction in hepatic venous outflow and to post-sinusoidal hypertension, resulting in clinical signs and symptoms[1,3]

MOST COMMON SIGNS AND SYMPTOMS OF VOD[3,9]

- Excessive platelet transfusions consistent with refractory thrombocytopenia
- Weight gain due to fluid retention
- Hepatomegaly
- Right upper quadrant pain
- Elevated bilirubin
- Elevated serum transaminase and alkaline phosphatase
- Ascites

Vigilant monitoring for the first 21 DAYS after HSCT is critical to detect VOD. Although VOD generally emerges within the first 21 days, it can occur later.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

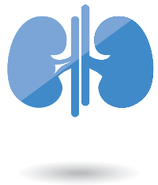
Hypersensitivity Reactions—Hypersensitivity reactions including rash, urticaria, and angioedema have occurred in less than 2% of patients treated with Defitelio. One case of an anaphylactic reaction was reported in a patient who had previously received Defitelio. Monitor patients for hypersensitivity reactions, especially if there is a history of previous exposure. If a severe hypersensitivity reaction occurs, discontinue Defitelio, treat according to the standard of care, and monitor until symptoms resolve.

Please see additional Important Safety Information on back and accompanying full Prescribing Information.

Progression of VOD can lead to renal or pulmonary dysfunction, which may be life threatening

Be alert for signs of renal or pulmonary dysfunction

RENAL DYSFUNCTION MAY INCLUDE[10-13]



- **Decreased urinary output**
- **Elevated creatinine levels (≥1.5 x baseline)**
- **Decreased creatinine clearance**
- **Decreased glomerular filtration rate**
- **Need for dialysis**

PULMONARY DYSFUNCTION MAY INCLUDE[11,12,14]

- **Pulmonary infiltrates**
- **Pleural effusion**
- **Reduced oxygen saturation**
- **Need for supplemental oxygen support (nasal cannula)**
- **Ventilator dependence**

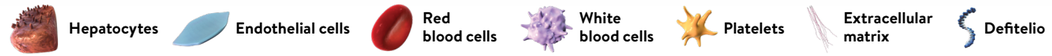
As VOD progresses to hepatorenal dysfunction, reversal of portal venous outflow may occur, this change in portal circulation is a late-stage finding of VOD.[1,3]

84% overall mortality in VOD with multi-organ dysfunction[8,a]

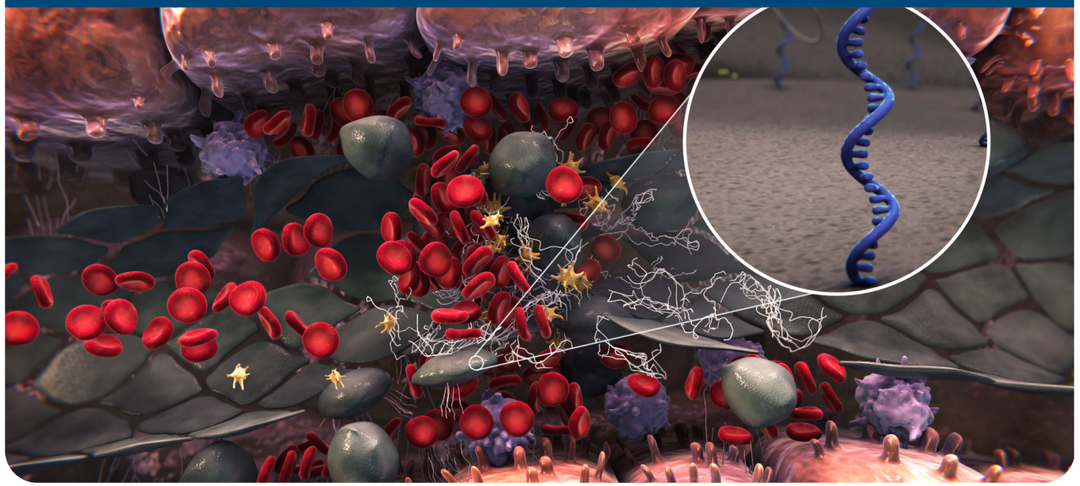
[a]Based on 19 studies (235 patients) that specifically determined mortality from severe VOD, as reported within a meta-analysis of 135 studies performed between 1979 and 2007.

Proposed mechanism of action of Defitelio

Preclinical studies have shown that Defitelio acts at multiple points across the VOD cascade[15-17,a]



ENDOTHELIAL CELL PROTECTION



Defitelio reduced sinusoidal endothelial cell activation by altering the expression of multiple factors (table B).[15]

Defitelio protected endothelial cells from damage caused by[15]:

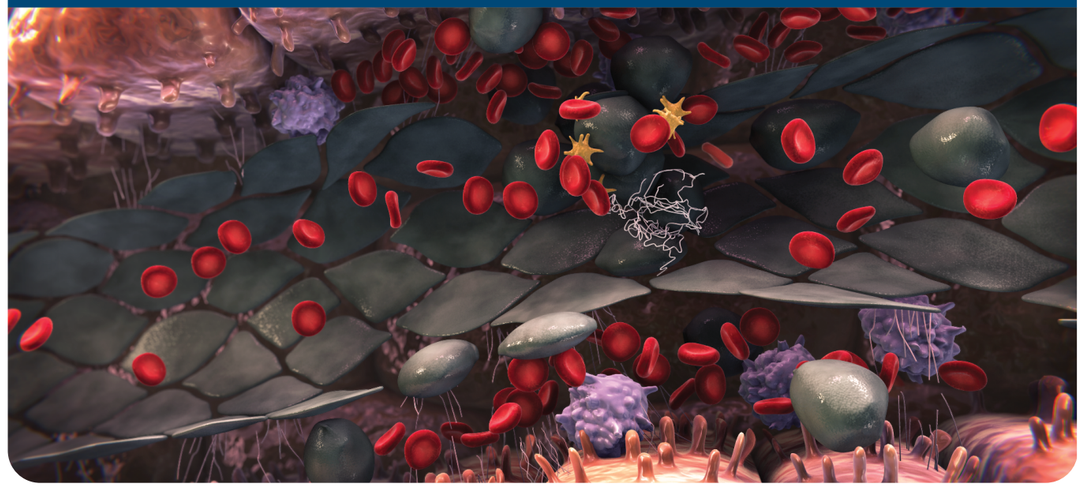
- Chemotherapy
- Tumor necrosis factor-α
- Serum starvation
- Perfusion

B. EFFECTS OF DEFITELIO[2,6,15,16,18]

Factor	Function	Defitelio action
Tissue plasminogen activator	catalyzes conversion of plasminogen to plasmin	↑
Thrombomodulin	anticoagulant cofactor	↑
von Willebrand factor	stimulates platelet aggregation	↓
Plasminogen activator inhibitor-1	reduces fibrinolysis	↓

[a]The mechanism of action of Defitelio has not been fully elucidated.

STABILIZATION WITH FIBRINOLYSIS



Defitelio promoted endothelial cell proliferation and partial revascularization of the sinusoid.[19]

Defitelio enhanced the enzymatic activity of plasmin to hydrolyze fibrin clots.[15]

Defitelio increased endothelial cell–mediated fibrinolysis via modulation of several factors (table B).[15]

Defitelio protects and stabilizes by restoring endothelial cell homeostasis and thrombotic-fibrinolytic balance, ultimately improving hepatic microvascular circulation[16,20]

IMPORTANT SAFETY INFORMATION

Most Common Adverse Reactions

The most common adverse reactions (incidence ≥10% and independent of causality) with Defitelio treatment were hypotension, diarrhea, vomiting, nausea, and epistaxis.

Please see additional Important Safety Information on back and accompanying full Prescribing Information.

DEFITELIO® (defibrotide sodium) injection 80 mg/mL

DEFITELIO® (defibrotide sodium) injection 80 mg/mL

Indication

Defitelio® (defibrotide sodium) 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).

IMPORTANT SAFETY INFORMATION

Contraindications

Defitelio is contraindicated in the following conditions:

- Concomitant administration with systemic anticoagulant or fibrinolytic therapy
- Known hypersensitivity to Defitelio or to any of its excipients

Warnings and Precautions

Hemorrhage

Defitelio may increase the risk of bleeding in patients with VOD after HSCT. Do not initiate Defitelio in patients with active bleeding. Monitor patients on Defitelio for signs of bleeding. If bleeding occurs, withhold or discontinue Defitelio.

Concomitant systemic anticoagulant or fibrinolytic therapy may increase the risk of bleeding and should be discontinued prior to Defitelio treatment. Consider delaying Defitelio administration until the effects of the anticoagulant have abated.

Hypersensitivity Reactions

Hypersensitivity reactions including rash, urticaria, and angioedema have occurred in less than 2% of patients treated with Defitelio. One case of an anaphylactic reaction was reported in a patientwho had previously received Defitelio. Monitor patients for hypersensitivity reactions, especiallyif there is a history of previous exposure. If a severe hypersensitivity reaction occurs, discontinue Defitelio, treat according to the standard of care, and monitor until symptoms resolve.

Most Common Adverse Reactions

The most common adverse reactions (incidence ≥10% and independent of causality) with Defitelio treatment were hypotension, diarrhea, vomiting, nausea, and epistaxis.

Please see accompanying full Prescribing Information.

References: 1. Richardson PG, Ho VT, Cutler C, et al. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: novel insights to pathogenesis, current status of treatment, and future directions. *Biol Blood Marrow Transplant*. 2013;19(suppl 1):S88-S90. **2.** Richardson PG, Corbacioglu S, Ho VT, et al. Drug safety evaluation of defibrotide. *Expert Opin Drug Saf.* 2013;12(1):123-136. **3.** Carreras E. Early complications after HSCT. In: Apperley J, Carreras E, Gluckman E, et al, eds. *The EBMT Handbook*. 6th ed. Paris, France: European School of Haematology; 2012:176-195. **4.** Vion AC, Rautou PE, Durand F, et al. Interplay of inflammation and endothelial dysfunction in bone marrow transplantation: focus on hepatic veno-occlusive disease. *Semin Thromb Hemost*. 2015;41(6):629-643. **5.** DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). *Semin Liver Dis.* 2002;22(1):27-41. **6.** Coppell JA, Brown SA, Perry DJ. Veno-occlusive disease: cytokines, genetics, and haemostasis. *Blood Rev.* 2003;17(2): 63-70. **7.** Bearman SI. The syndrome of hepatic veno-occlusive disease after marrow transplantation. *Blood*. 1995;85(11):3005-3020. **8.** Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. *Biol Blood Marrow Transplant*. 2010;16(2):157-168. **9.** Cairo MS, Cooke KR, Lazarus HM, Chao N. Modified diagnostic criteria, grading classification and newly elucidated pathophysiology of hepatic SOS/VOD after haematopoietic cell transplantation. *Br J Haematol.* 2020;190(6):822-836. **10.** Mohty M, Malard F, Abecassis M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2016;51(7):906-912. **11.** Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood*. 2016;127(13):1656-1665. **12.** Richardson PG, Murakami C, Jin Z, et al. Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. *Blood*. 2002;100(13):4337-4343. **13.** Ng CK, Chan MH, Tai MH, Lam C. Hepatorenal syndrome. *Clin Biochem Rev.* 2007;28(1):11-17. **14.** McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med*. 1993;118(4):255-267. **15.** Defitelio [package insert]. Palo Alto, CA: Jazz Pharmaceuticals. **16.** Richardson PG, Palomo M, Kernan NA, et al. The importance of endothelial protection: the emerging role of defibrotide in reversing endothelial injury and its sequelae. *Bone Marrow Transplant*. 2021;56(12):2889-2896. **17.** Scalia R, Kochilas L, Campbell B, Lefer AM. Effects of defibrotide on leukocyte-endothelial cell interaction in the rat mesenteric vascular bed: role of P-selectin. *Meth Find Exp Clin Pharmacol*. 1996;18(10):669,676. **18.** Yau JW, Teoh H, Verma S. Endothelial cell control of thrombosis. *BMC Cardiovasc Disord*. 2015;15:130. **19.** Benimetskaya L, Wu S, Voskresenskiy AM, et al. Angiogenesis alteration by defibrotide: implications for its mechanism of action in severe hepatic veno-occlusive disease. *Blood*. 2008;112(10):4343-4352. **20.** Richardson PG, Grupp SA, Pagliuca A, et al. Defibrotide for the treatment of hepatic veno-occlusive disease/sinusoidal obstruction syndrome with multiorgan failure. *Int J Hematol Oncol.* 2017;6(3):75-93.

Jazz Pharmaceuticals