

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrDEFITELIO™

Defibrotide sodium

Solution for Intravenous Infusion, 200 mg/2.5 mL (80 mg/mL)

Manufacturer's Standard

ATC: B01AX01

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DEFITELIO™
Defibrotide sodium

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Solution for intravenous infusion 200 mg/2.5 mL (80 mg/mL)	Sodium citrate dihydrate Hydrochloric acid (for pH adjustment) Sodium hydroxide (for pH adjustment) Water for injection

DESCRIPTION

DEFITELIO™ is an oligonucleotide mixture with profibrinolytic properties. Defibrotide sodium is a polydisperse mixture of predominantly single-stranded (ss) polydeoxyribonucleotide sodium salts derived from porcine intestinal tissue having a mean weighted molecular weight of 13-20 kDa, and a potency of 27-39 and 28-38 biological units per mg as determined by two separate assays measuring the release of a product formed by contact between defibrotide sodium, plasmin and a plasmin substrate. The chemical name of defibrotide sodium is polydeoxyribonucleotide, sodium salt.

DEFITELIO™ (defibrotide sodium) solution is a clear, light yellow to brown, sterile, preservative-free solution in a single-use vial for intravenous infusion. Each milliliter of the injection contains 80 mg of defibrotide sodium and 10 mg of Sodium Citrate, in Water for Injection. Hydrochloric Acid and/or Sodium Hydroxide, may have been used to adjust pH to 6.8-7.8.

INDICATIONS AND CLINICAL USE

DEFITELIO™ (defibrotide sodium) solution for intravenous infusion 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 haematopoietic stem-cell transplantation (HSCT) therapy.

Geriatrics (> 65 years of age):

Clinical studies of DEFITELIO™ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Pediatrics (≤ 16years of age):

The safety and effectiveness of DEFITELIO in pediatric patients (≥ 1 month to < 16 years of age) were established in clinical trials pediatric patients with severe hepatic VOD following HSCT.

CONTRAINDICATIONS

- Concomitant administration with systemic anti-coagulant or fibrinolytic therapy.
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the [Dosage Forms, Composition and Packaging](#) section of the product monograph.

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

DEFITELIO™ must be prescribed and administered to patients by specialised physicians experienced in the diagnosis and treatment of complications of HSCT.

DEFITELIO increased the activity of thrombolytic/fibrinolytic enzymes *in vitro*, and it may increase the risk of bleeding in patients with VOD after HSCT (see [WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS](#) Sections). Do not initiate DEFITELIO in patients with active bleeding.

Patients should be closely monitored for signs and symptoms of haemorrhage during treatment with DEFITELIO. In patients who develop active bleeding, discontinue treatment with DEFITELIO until the bleeding is controlled. Discontinue DEFITELIO infusion at least 2 hours prior to an invasive procedure.

Patients treated with DEFITELIO must not receive concomitant medications such as heparin, warfarin, alteplase, or other systemic anticoagulant or fibrinolytic therapy (excluding routine maintenance or reopening of central venous lines) because of the potential increased risk of bleeding.

Hematologic*Haemorrhage /Bleeding*

DEFITELIO increased the activity of thrombolytic/fibrinolytic enzymes *in vitro*, and it may increase the risk of bleeding in patients with severe VOD after HSCT.

Concomitant use of defibrotide sodium and systemic anticoagulant or thrombolytic/fibrinolytic therapy (excluding routine maintenance or reopening of central venous lines) may increase the risk of bleeding. Discontinue systemic anticoagulant or thrombolytic/fibrinolytic therapy prior to

starting defibrotide sodium therapy and consider delaying the start of defibrotide sodium administration until the effects of the anticoagulant or thrombolytic/fibrinolytic therapy have abated (see [Drug-Drug Interactions](#) section). Concomitant use of DEFITELIO and antiplatelet therapy requires careful monitoring/close medical supervision.

Do not initiate DEFITELIO™ in patients with active and/or clinically significant bleeding. Temporary discontinuation of DEFITELIO is recommended in patients who undergo surgery or invasive procedures. Monitor patients for signs of bleeding. If patients on DEFITELIO develop bleeding, discontinue DEFITELIO, treat the underlying cause, and provide supportive care until the bleeding is stopped.

Hemodynamic Instability

Prior to administration of DEFITELIO, confirm that the patient is hemodynamically stable on no more than one vasopressor.

Immune

Anaphylactic reaction has been reported in association with the use of DEFITELIO. Monitor patients for severe hypersensitivity reactions, especially if there is a history of previous exposure to defibrotide sodium. If a severe hypersensitivity reaction occurs, discontinue DEFITELIO permanently; do not resume treatment.

Peri-Operative Considerations/Surgery

There is no known reversal agent for the profibrinolytic effects of DEFITELIO™. Discontinue DEFITELIO infusion at least 2 hours prior to an invasive procedure. Resume DEFITELIO treatment after the procedure, as soon as any procedure-related risk of bleeding is resolved.

Special Populations

Pregnant Women:

There are no available data on defibrotide sodium use in pregnant women. DEFITELIO use during pregnancy is not recommended. Animal toxicology studies with DEFITELIO in pregnant rats and rabbits revealed a high rate of haemorrhagic abortion.

Nursing Women:

There is no information regarding the presence of defibrotide sodium in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions, including bleeding in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with DEFITELIO.

Fertility:

There are no studies investigating the effects of defibrotide sodium on human fertility.

Given the short half-life of defibrotide sodium and negative genotoxic studies effective contraception is required for male and female patients during exposure to DEFITELIO™ and for one week subsequent to discontinuation.

Pediatrics (≤ 16 years of age):

The safety and effectiveness of DEFITELIO have been established in pediatric patients age >1 month. The safety and efficacy of DEFITELIO in children aged less than 1 month have not yet been established and no clinical data are available in this patient population. The use of DEFITELIO in children aged less than one month is not recommended.

Geriatrics (> 65 years of age):

The safety and effectiveness of DEFITELIO have not been established in the geriatric population. Overall, the number of patients age 65 and over in clinical trials was not sufficient to determine whether they respond differently from younger patients.

ADVERSE REACTIONS**Adverse Drug Reaction Overview**

The most common adverse events (incidence \geq 10% and independent of causality) reported in Studies 1 and 2 (N=176) were hypotension, diarrhea, vomiting, nausea, and epistaxis. The most common serious adverse events (incidence \geq 5% and independent of causality) reported in Studies 1 and 2 were hypotension (11%) and pulmonary alveolar haemorrhage (7%). See [Table 2 in CLINICAL TRIALS, Study Demographics and Trial Design](#).

Information about adverse events resulting in permanent discontinuation of DEFITELIO was available for 102 patients from Study 1, and 35 (34%) of these patients had an adverse event with permanent discontinuation. Adverse events leading to permanent discontinuation included pulmonary alveolar haemorrhage in 5 (5%) patients; pulmonary haemorrhage, hypotension, catheter site haemorrhage, and multi-organ failure, each in 3 (3%) patients; and cerebral haemorrhage and sepsis, each in 2 (2%) patients.

Haemorrhagic adverse events, any grade, were reported in 57% of patients in Studies 1 and 2 compared to 75% of patients in the Historical Control group. The most commonly reported haemorrhagic adverse events in Studies 1 and 2 were epistaxis (14% vs. 16%, DEFITELIO™ vs. Historical Control), pulmonary alveolar haemorrhage (9% vs. 16%), hematuria (9% vs. 16%) and gastrointestinal haemorrhage (9% vs. 9%). Severe or life-threatening haemorrhagic adverse events occurred in 29% of DEFITELIO patients (grading of events was not available for Historical Control patients). Haemorrhagic adverse events that led to death occurred in 9% of DEFITELIO patients in Studies 1 and 2 and in 6% of Historical Control patients. See [Warnings and Precautions](#).

Adverse events potentially associated with hypersensitivity to DEFITELIO for which no alternate etiology was provided were seen in five patients in clinical trials. Post-marketing surveillance has reported one case of anaphylactic shock and another of hypersensitivity.

The frequency, nature and severity of adverse events in children were similar to adults. Pediatric patients had a similar incidence of overall haemorrhage compared with adults. No special precautions are indicated in pediatric patients.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety information presented in [Table 1](#) is based on 176 patients who received DEFITELIO for the treatment of VOD with multi-organ failure (MOF) following HSCT at the recommended dose of 25 mg/kg/day in Studies 1 and 2. The median age of the safety population was 25 years (range 1 month to 72 years), and 63% were ≥ 17 years of age. A total of 60% of patients were male, 78% were white, 89% had undergone allogeneic HSCT, and the underlying diagnosis was acute leukemia for 43%. At study entry, 13% were dialysis dependent and 18% were ventilator dependent.

Patients were excluded from these trials if, at time of study entry, they had significant acute bleeding or required the use of any medications that could increase the risk of haemorrhage, or had active grades B-D graft-versus-host disease or haemodynamic instability (required multiple vasopressors to provide blood pressure support). DEFITELIO was administered for a median of 21 days (range: 1 to 83 days).

In Study 1 and Study 2 (N=176) overall rates for any type of haemorrhage were similar for pediatric (58.5%) and for adult (56.8%) patients treated with DEFITELIO. In Study 1 and Study 2 for pediatric patients treated with DEFITELIO at a dose of 25 mg/kg/day pulmonary alveolar haemorrhage and pulmonary haemorrhage were reported in 15% and 9% of patients which is similar to that of the control. In adult patients the rates were numerical lower with 5% of adult patients reporting pulmonary alveolar haemorrhage and 1% reporting pulmonary haemorrhage.

Among the 176 patients who received DEFITELIO for the treatment of VOD with MOF following HSCT at the recommended dose of 25 mg/kg/day in Studies 1 and 2, 128 patients died during the study period. The most common causes of death (incidence $\geq 5\%$) reported in Study 1 and Study 2 were progression of VOD, infection, and bleeding.

For the purposes of adverse event recording in the clinical trials, events were not required to be reported if they were related to the hepatic veno-occlusive disease, or if they were expected to occur after hematopoietic stem-cell transplantation (HSCT), unless they were serious or Grade 4-5.

Table 1: Related Treatment-Emergent Adverse Events (TEAEs) (Adverse Drug Reactions) Reported in ≥ 1% of Patients in Studies 1 and 2 (VOD with MOF post-HSCT, 25 mg/kg/day), N=176

System Organ Class/ Preferred Term, n (%)	Defibrotide sodium 25 mg/kg
Number of patients	176
With at least 1 related TEAE	58 (33.0)
Blood and lymphatic system disorders	2 (1.1)
Coagulopathy	2 (1.1)
Eye disorders	2 (1.1)
Conjunctival haemorrhage	2 (1.1)
Gastrointestinal disorders	21 (11.9)
Gastrointestinal haemorrhage	7 (4.0)
Diarrhea	4 (2.3)
Nausea	3 (1.7)
Vomiting	3 (1.7)
General disorders and administration site conditions	5 (2.8)
Catheter site haemorrhage	3 (1.7)
Injury, poisoning, and procedural complications	5 (2.8)
Post procedural haemorrhage	5 (2.8)
Nervous system disorders	8 (4.5)
Central nervous system haemorrhage	2 (1.1)
Cerebral haemorrhage	2 (1.1)
Headache	2 (1.1)
Renal and urinary disorders	2 (1.1)
Hematuria	2 (1.1)
Respiratory, thoracic, and mediastinal disorders	21 (11.9)
Pulmonary alveolar haemorrhage	10 (5.7)
Epistaxis	8 (4.5)
Pulmonary haemorrhage	2 (1.1)
Skin and subcutaneous tissue disorders	6 (3.4)
Ecchymosis	3 (1.7)
Petechiae	2 (1.1)
Pruritus	2 (1.1)
Rash	2 (1.1)
Vascular disorders	11 (6.3)
Hypotension	10 (5.7)

Less Common Clinical Trial Related Adverse Events (Adverse Drug Reactions) (<1%)

Gastrointestinal disorders: hematemesis, upper gastrointestinal haemorrhage, gastric haemorrhage, hematochezia, melena, mouth haemorrhage

General disorders and administration site conditions: chills, feeling hot, puncture site haemorrhage

Investigations: international normalized ratio increased

Nervous system disorders: lethargy, spinal hematoma, subarachnoid haemorrhage, subdural hygroma

Reproductive system and breast disorders: menorrhagia

Respiratory, thoracic and mediastinal disorders: hemothorax, thoracic haemorrhage
Skin and subcutaneous tissue disorders: dry skin, pruritus generalized, purpura, skin haemorrhage

Vascular disorders: flushing, haemorrhage, hematoma.

Abnormal Hematologic and Clinical Chemistry Findings

There were no safety concerns for DEFITELIO revealed from clinical laboratory results. Changes in laboratory values were generally consistent with underlying disease and veno-occlusive disease diagnosis.

In one study, the following notable differences between defibrotide sodium and control groups regarding change from baseline were:

- Total bilirubin and direct bilirubin minimally increased in defibrotide sodium group with larger increases in the historical control
- AST and ALT decreased in the defibrotide sodium group, increased in the historical control
- BUN decreased in the defibrotide sodium group but increased in the historical control

Post-Market Adverse Drug Reactions

Based on the review of the literature, DEFITELIO™ has been generally well tolerated, and the overall safety profile of DEFITELIO appears to be acceptable. The principal toxicity of concern is the potential for increased risk of haemorrhage. Although many reports have noted an absence of clinically significant haemorrhage with defibrotide sodium, an increased risk has been noted in other reports. In a few patients, hemorrhage has been severe. One case of anaphylactic reaction was reported in a patient who had previously received DEFITELIO; monitoring for hypersensitivity reactions is warranted.

DRUG INTERACTIONS

Overview

Pharmacokinetic drug-drug interactions are unlikely at the therapeutic dose of defibrotide sodium. Data from *in vitro* studies using human biomaterials demonstrate that defibrotide sodium does not induce (CYP1A2, CYP2B6, CYP3A4, UGT1A1) or inhibit (CYP1A2, CYP2B6, CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT1A1, UGT2B7) the major drug metabolizing enzymes and is not a substrate or inhibitor of the major drug uptake transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3) or efflux transporters (P-gp and BCRP). There is some evidence (animal studies, *ex vivo* human plasma, and healthy volunteers) that defibrotide sodium may enhance the pharmacodynamic activity of heparin and alteplase.

Drug-Drug Interactions

Antithrombotic Agents

Defibrotide sodium may enhance the pharmacodynamic activity of antithrombotic/fibrinolytic drugs such as heparin or alteplase. Concomitant use of defibrotide sodium with anticoagulant or fibrinolytic drugs is contraindicated because of an increased risk of haemorrhage. There is some evidence (animal studies, *ex vivo* human plasma, and healthy volunteers) that defibrotide sodium may enhance the pharmacodynamic activity of heparin and alteplase.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Administer DEFITELIO™ for a minimum of 21 days. If after 21 days signs and symptoms of hepatic VOD have not resolved, continue DEFITELIO until resolution of VOD.

Prior to administration of DEFITELIO, confirm that the patient is not experiencing clinically significant bleeding and is haemodynamically stable on no more than one vasopressor.

Recommended Dose and Dosage Adjustment

The recommended dose of DEFITELIO is 25 mg/kg/day administered as 6.25 mg/kg every 6 hours given as a 2-hour intravenous infusion. Dosing should be based on patient's baseline body weight, defined as the patient's weight prior to the preparative regimen for HSCT.

Renal Impairment

No dosage adjustment is needed for patients with renal impairment or who are on hemodialysis.

Hepatic Impairment

No dosage adjustment is needed for patients with hepatic impairment.

Paediatric population

No dose adjustments are needed for pediatric patients.

Administration

DEFITELIO™ must be diluted prior to infusion. DEFITELIO should be administered by constant intravenous infusion over a 2-hour period. Do not co-administer DEFITELIO and other intravenous drugs concurrently within the same intravenous line. The diluted DEFITELIO solution should be administered using an infusion set equipped with a 0.2 micron in-line filter. The intravenous administration line (peripheral or central) should be flushed with 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, immediately before and after administration.

Reconstitution:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard vial if either is present.

Dilute DEFITELIO™ with either 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, to a concentration of 4 mg/mL to 20 mg/mL. Administer the diluted solution over 2 hours. The total dose and volume of infusion should be determined based on the individual patient's baseline weight (weight prior to the preparative regimen for HSCT).

Vials contain no antimicrobial preservatives and are intended for a single use only. Partially used vials should be discarded. The diluted DEFITELIO solution should be used within 4 hours if stored at room temperature or within 24 hours if stored at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Up to four doses may be prepared at one time.

Preparation Instructions:

- Determine the dose (mg) and number of vials of DEFITELIO based on the individual patient's baseline weight (kg) (weight prior to the preparative regimen for HSCT).
- Calculate the volume of DEFITELIO needed. Using appropriate aseptic technique withdraw this amount from the vial(s) and add it to the infusion bag containing 5% Dextrose Injection or 0.9% Sodium Chloride Injection for each dose to make a final concentration of 4 mg/mL to 20 mg/mL.
- Gently mix the solution for infusion.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Only clear solutions without visible particles should be used. Depending on the type and amount of diluent, the color of the diluted solution may vary from colorless to light yellow. It is recommended that the diluted DEFITELIO solution be administered to patients using an infusion set equipped with a 0.2 micron in-line filter.
- Partially used vials should be discarded.
- Use the diluted DEFITELIO solution within 4 hours if stored at room temperature or within 24 hours if stored under refrigeration.

OVERDOSAGE

There is no antidote for DEFITELIO™ and DEFITELIO is not dialyzable. If an overdose occurs, general supportive measures should be instituted.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of defibrotide sodium has not been fully elucidated. *In vitro* data support a role for defibrotide sodium in both endothelial cell (EC) protection and the restoration of the thrombo-fibrinolytic balance. *In vitro*, defibrotide sodium enhances the enzymatic activity of plasmin to hydrolyze fibrin clots. Studies evaluating the pharmacological effects of defibrotide sodium on endothelial cells (ECs) were conducted primarily in the human microvascular endothelial cell line. *In vitro*, defibrotide sodium increased tissue plasminogen activator (t-PA) and thrombomodulin expression, and decreased von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1) expression, thereby reducing EC activation and increasing EC-mediated fibrinolysis. Defibrotide sodium protected ECs from damage caused by chemotherapy, tumor necrosis factor- α (TNF- α), serum starvation, and perfusion.

Pharmacodynamics

Cardiac Electrophysiology

At a dose 2.4 times the maximum recommended dose, DEFITELIO does not prolong the QTc interval to any clinically relevant extent.

PAI-1 Inhibition

Plasma concentrations of PAI-1 were assessed on an exploratory basis as a potential pharmacodynamic marker for efficacy in a clinical study. PAI-1 is an inhibitor of t-PA and therefore of fibrinolysis. Mean PAI-1 levels on Days 7 and 14 were lower than those at baseline in patients with complete response (CR) and in those who were alive at Day+100, but this trend did not reach statistical significance. There were no statistically significant differences in mean PAI-1 levels by treatment or outcome.¹

Pharmacokinetics

Absorption:

After intravenous administration, peak plasma concentrations of defibrotide sodium occur approximately at the end of each infusion.

Distribution:

Defibrotide sodium is highly bound to human plasma proteins (average 93%) and has a volume of distribution of 8.1 to 9.1 L.

Elimination:

Metabolism followed by urinary excretion is likely the main route of elimination. The estimated total clearance was 3.4 to 6.1 L/h. The elimination half-life of defibrotide sodium is less than 2 hours. Similar plasma concentration profiles were observed in severe VOD patients after initial and multiple-dose administration of 6.25 mg/kg every 6 hours for 5 days. Therefore, no accumulation is expected following multiple-dose administration.

Metabolism:

Though the precise pathway of defibrotide sodium degradation in plasma *in vivo* is largely unknown, it has been suggested that nucleases, nucleotidases, nucleosidases, deaminases, and phosphorylases metabolize polynucleotides progressively to oligonucleotides, nucleotides, nucleosides, and then to the free 2'-deoxyribose sugar, purine and pyrimidine bases.

The biotransformation of defibrotide sodium was investigated *in vitro* by incubation with human hepatocytes from donors of different ages and showed that defibrotide sodium does not undergo appreciable metabolism by human hepatocyte cells.

Excretion:

After administration of 6.25 mg/kg to 15 mg/kg doses of DEFITELIO™ as 2-hour infusions, approximately 5-15% was excreted in urine as defibrotide sodium, with the majority excreted during the first 4 hours.

Special Populations and Conditions**Pediatrics:**

Insufficient PK data were collected in pediatric patients to draw conclusions.

Geriatrics:

The pharmacokinetics of DEFITELIO have not been established in the geriatric population.

Hepatic Insufficiency:

The Phase 3 (Study 1) and Phase 2 (Study 2) trials enrolled patients with severe hepatic VOD including multi-organ dysfunction. Hepatic impairment is integral to the diagnosis of severe hepatic VOD. As the approved dosing regimen was evaluated in the presence of hepatic impairment, dose-adjustment is not indicated in this population.

Renal Insufficiency:

The safety, tolerability, and pharmacokinetics of 6.25 mg/kg as 2-hour intravenous infusions of defibrotide sodium were evaluated in subjects with hemodialysis-dependent end-stage renal disease (ESRD) during hemodialysis and on days off dialysis (n=6), subjects with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73m²) or ESRD not requiring hemodialysis (n=6), and subjects with normal renal function (n=6). Defibrotide sodium was not removed by hemodialysis, which had no notable effect on plasma clearance of defibrotide sodium. Terminal half-lives were consistently less than 2 hours, and there was no accumulation

of defibrotide sodium following repeated dosing. Defibrotide sodium exposure (AUC) was 50% to 60% higher and peak concentration (C_{max}) was 35% to 37% higher in subjects with severe renal impairment or ESRD than in subjects with normal renal function following single- and multiple-dose administration of defibrotide sodium.

STORAGE AND STABILITY

Shelf life stability of unopened vials: 36 months

Store unopened vials at 20°C-25°C; excursions permitted between 15°C to 30°C. Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

DEFITELIO™, once diluted, should be used within 24 hours when stored at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Do not re-use partially used vials.

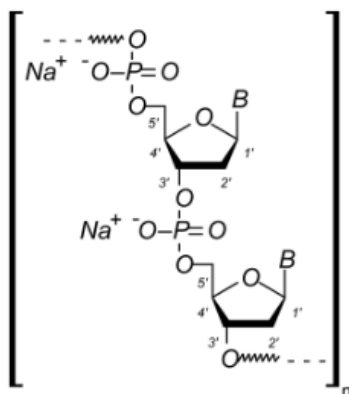
DOSAGE FORMS, COMPOSITION AND PACKAGING

DEFITELIO is supplied in a single-use, clear glass vial. Each carton of DEFITELIO contains 10 vials. Each single vial contains 200 mg/2.5 mL (concentration of 80 mg/mL) of defibrotide sodium, sodium citrate dihydrate and water for injection. Hydrochloric acid and/or, sodium hydroxide may have been used for pH adjustment.

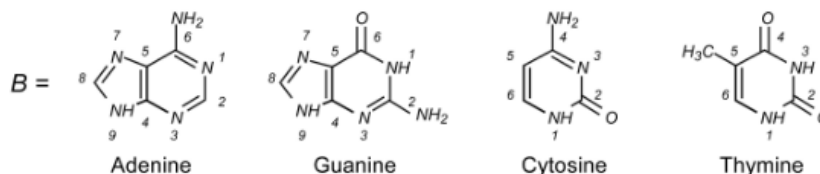
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Proper name: Defibrotide sodium
Chemical name: Polydeoxyribonucleotide, sodium salt
Molecular mass: 13-20 kDa
Structural formula:



$n = \text{from about 2 to 50}$



Physicochemical properties: Defibrotide sodium is a polydisperse mixture of predominantly single-stranded (ss) polydeoxyribonucleotide sodium salts derived from porcine intestinal tissue. It is a clear, light yellow to brown, sterile, preservative-free solution for intravenous infusion. Each single-use clear glass vial contains 2.5 mL of an 80 mg/mL solution of defibrotide sodium in aqueous sodium citrate injection. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.8-7.8.

CLINICAL TRIALS

The efficacy of DEFITELIO™ was investigated in two prospective studies (Study 1 and Study 2), and an expanded access study (Study 3).

In Study 1, 102 adult and pediatric patients with a diagnosis of VOD according to the following criteria (bilirubin of at least 2 mg/dL and at least two of the following findings: hepatomegaly, ascites, and weight gain greater than 5% by Day+21 post-HSCT) with an associated diagnosis of multi-organ dysfunction (pulmonary, renal, or both) by Day+28 post-HSCT were treated with DEFITELIO. Treatment was administered at a dose of 6.25 mg/kg infused every 6 hours for a minimum of 21 days and continued until patient was discharged from the hospital. Patients treated with DEFITELIO were not permitted to receive concomitant medications such as heparin, warfarin, or alteplase because of an increased risk of bleeding.

In Study 2, 75 adult and pediatric patients with a diagnosis of hepatic VOD and multi-organ dysfunction following HSCT were treated with DEFITELIO at a dose of 6.25 mg/kg infused every 6 hours. The planned minimum duration of treatment was 14 days. The treatment could be continued until signs of hepatic VOD resolved.

In Study 3, the efficacy of DEFITELIO was evaluated in 351 adult and pediatric patients who had received a HSCT and developed hepatic VOD with renal or pulmonary dysfunction. All patients received DEFITELIO at a dose of 6.25 mg/kg infused every 6 hours.

Table 2 provides baseline demographic for patients treated with DEFITELIO in these studies.

Table 2: Baseline Demographics of Patients Treated with DEFITELIO at 6.25 mg/kg Every 6 hours

Data Source	Study 1	Study 2	Study 3
Design	Prospective	Prospective	Expanded Access Study
Number of patients	102	75	351
Median age (years) (range)	21 years (< 1,72)	32 years (<1,61)	15 years (<1.69)
Age, n (%)			
< 17 years	44 (43%)	22 (29%)	189 (54%)
≥ 17 years	58 (57%)	53 (71%)	162 (46%)
Race, n (%)			
White	77 (75%)	61 (81%)	237 (68%)
Black/African American	6 (6%)	6 (8%)	21(6%)
Asian	4 (4%)	2 (3%)	15 (4%)
Other	15 (15%)	6 (8%)	78 (22 %)
Gender, n (%)			
Male	64 (63%)	41 (55 %)	184 (52%)
Female	38 (37%)	34 (45%)	167 (48%)
Median number of days on treatment (days) (range)	21.5 days (1,58)	19.5 days (3,83)	21.0 days ^a (1,93)
Type of graft, n (%)			
Allograft	90 (88%)	67 (89%)	317 (90%)

Data Source	Study 1	Study 2	Study 3
Autograft	12 (12%)	8 (11%)	34 (10%)
Ventilator or Dialysis Dependent at Study Entry, n (%)	34 (33%)	8 (11%)	149 (42%)

^a Duration of treatment from first dose to last dose is presented because days without treatment were not captured for the expanded access study.

The efficacy of DEFITELIO was based on survival at Day + 100 after HSCT. In Study 1, the survival rate was 38% (95% CI: 29%, 48%) at 100 days after transplantation. In Study 2, the survival rate was 44% (95% CI: 33%, 55%) at 100 days after transplantation. In Study 3, the Day + 100 survival rate was 45% (95% CI: 40%, 51%).

Based on published reports and analyses of patient level data for individuals with hepatic VOD with renal or pulmonary dysfunction who received supportive care or interventions other than DEFITELIO, the historical expected Day +100 survival rates were estimated to be between 21% and 31%.

DETAILED PHARMACOLOGY

In Vitro Studies

Based on the results of *in vitro* primary pharmacodynamic studies, DEFITELIO:

- Prevents or minimizes the cytotoxic effect of high cell density or serum starvation stress (but not oxidative stress) on endothelial cells;
- Protects endothelial cells from 5-fluorouracil- and fludarabine-mediated apoptosis and cell death, and from the pro-thrombotic effect of thalidomide, without affecting the efficacy of these chemotherapeutic agents;
- Exerts direct endothelial cell protection by reducing the mRNA level of caspase-3 and activated protein upon fludarabine-induced stress;
- Down-regulates fludarabine-induced genes, especially those associated with a pro-apoptotic phenotype, angiogenesis/migration, adhesion, and inflammatory activation (such as heparanase, interleukin-8, caspase-3, melanoma cell adhesion molecule, and major histocompatibility complex Class II);
- Augments the amidolytic activity of plasmin to help restore thrombo-fibrinolytic balance.

TOXICOLOGY

Animal Studies

Carcinogenicity

No carcinogenicity studies have been conducted with intravenous administration of defibrotide sodium. Defibrotide sodium was not mutagenic *in vitro* in a bacterial reverse mutation assay (Ames assay). Defibrotide sodium was not clastogenic in an *in vitro* chromosomal aberrations assay in Chinese hamster ovary cells or an *in vivo* micronucleus assay conducted in bone marrow from rats administered defibrotide sodium by intravenous infusion.

Impairment of Fertility

Studies of fertility were not conducted with defibrotide sodium administered by the intravenous route. In repeat dose general toxicology studies, when defibrotide sodium was administered intravenously to rats and dogs for up to 13 weeks, there were no effects on male or female reproductive organs.

Developmental Toxicity

Embryo-fetal toxicity assessment was attempted in rats and rabbits, but was not possible because of high maternal mortality, abortion, and fetal resorption at all doses. Pregnant rats were administered defibrotide sodium from gestational day (GD) 6 to 15 at 0, 240, 1200, and 4800 mg/kg/day by continuous intravenous infusion over 24 hours or at 60, 120, and 240 mg/kg/day by 2-hour infusions 4 times per day. Pregnant rabbits were administered defibrotide sodium at 0, 30, 60, or 120 mg/kg/day from GD 6 to 18 by 2 hour infusions 4 times per day.

In another study in pregnant rabbits, 3 separate subgroups of animals were treated with doses of 80 mg/kg/day defibrotide sodium administered by 2-hour infusions 4 times per day for 5 days each in a staggered manner during the organogenesis period. The dose of 80 mg/kg/day is approximately equivalent to the recommended clinical dose on a mg/m² basis. Subgroup 1 was dosed from GD 6 to 10, subgroup 2 was dosed from GD 10 to 14, and subgroup 3 was dosed from GD 14 to 18. An increased incidence of unilateral implantation was observed in defibrotide sodium-treated animals. Treatment with defibrotide sodium resulted in a decreased number of implantations and viable fetuses.

A juvenile toxicity study in 21-day-old rats was conducted with intravenous bolus administration of defibrotide sodium at 40, 150, or 320 mg/kg/day for 4 weeks. A delayed mean age of preputial separation was observed at all doses, suggesting a delay in onset of male puberty. The dose of 40 mg/kg/day is approximately 0.4 times the clinical dose on a mg/m² basis for a child. The relevance of this finding for the onset of male puberty in humans is unknown.

Toxicity

In the 13-week toxicity studies in rats and dogs, intravenous administration of defibrotide sodium transiently prolonged activated partial thromboplastin time (APTT) at 1200 and 4800 mg/kg/day administered as a continuous infusion in rats and at 300 and 1600 mg/kg/day administered in 2-hour infusions 4 times daily in dogs. Prothrombin time (PT) was also transiently increased at 4800 mg/kg/day in rats. These findings were observed at doses at least 6 times higher on a

mg/m² basis than the clinical dose of 25 mg/kg/day. The effects on APTT and PT may be due to direct effects on coagulation based on the dose-dependent response observed.

REFERENCES

1. Richardson PG, Soiffer RJ, Antin JH, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. *Biol Blood Marrow Transplant.* 2010 Jul;16(7):1005-17