PACKAGE INSERT
DEFITELIO®(defibrotide)
CONCENTRATE FOR SOLUTION FOR INFUSION
200MG/2.5ML

1. NAME OF THE MEDICINE

Defibrotide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of concentrate contains defibrotide* 80 mg corresponding to a quantity of 200 mg in 2.5 mL in a vial before dilution. The final concentration of the solution should be in the range of 4 mg/mL to 20 mg/mL after dilution.

* produced from porcine intestinal mucosa.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

The solution is clear light yellow to brown, free from particulate matter or turbidity.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Defitelio is indicated for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy.

It is indicated in adults and in adolescents, children and infants of 1 month of age and above.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Dosage

The recommended dose is 6.25 mg/kg body weight every 6 hours (25 mg/kg/day).

There is limited efficacy and safety data on doses above this level and consequently it is not recommended to increase the dose above 25 mg/kg/day.

The treatment should be administered for a minimum of 21 days and continued until the symptoms and signs of severe VOD resolve.

Dose adjustment

Renal impairment

Dose adjustment is not required for patients with renal impairment or who are on intermittent haemodialysis (see section 5.2 Pharmacokinetic properties – Special populations).

Hepatic impairment

No formal pharmacokinetic studies have been performed in patients with hepatic impairment; however, the medicinal product has been used in clinical trials of patients developing hepatic impairment without dose adjustment with no safety issues identified. No dose adjustment is therefore recommended but careful monitoring of patients should be undertaken (see section 5.2 Pharmacokinetic properties – Special populations).

Paediatric population

The recommended dose for children aged 1 month and above to 18 years is the same mg/kg dose as for adults i.e. 6.25 mg/kg body weight every 6 hours.

The safety and efficacy of defibrotide in children aged less than 1 month have not yet been established. No data are available. The use of Defitelio in children aged less than one month is not recommended.

Method of administration

Defitelio is for intravenous use. It is administered by intravenous infusion, over two hours.

Defitelio should always be diluted prior to use. It can be diluted with 5% glucose solution for infusion or sodium chloride 9 mg/mL (0.9%) solution for infusion (see section 6.3 for concentration range and stability of the diluted solution), to a suitable concentration to permit infusion over 2 hours. The total volume of infusion should be determined based on the individual patient's weight. The final concentration of Defitelio should be in the range of 4 mg/mL to 20 mg/mL.

Vials are intended for a single use and unused solution from a single dose must be discarded (see section 6.6 Special precautions for disposal)

The concentrate for solution for infusion must be diluted using aseptic technique.

Preparation of Defitelio (use aseptic technique):

1. The total dose and thereby, the total volume of infusion and the total number of vials to be diluted should be determined based on the individual patient's weight. The final concentration of Defitelio should be in the concentration range of 4 mg/mL – 20 mg/mL (see section 6.3 Shelf life).
2. Before dilution, each vial should be inspected for particles. If particles are observed and/or the liquid in the vial is not clear, the vial must not be used.
3. The required volume from the Defitelio vials should be withdrawn and combined.
4. A volume of the sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose 5% solution for infusion from the infusion bag, equal to the total volume of Defitelio concentrate for solution for infusion to be added, should be withdrawn and discarded.
5. The combined volumes of Defitelio should be added to the sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose 5% solution for infusion.

6. The solution for infusion should be mixed gently.

7. Prior to use the solution should be visually inspected for particulate matter. Only clear solutions without visible particles should be used. Depending on the type and amount of diluent the colour of the diluted solution may vary from colourless to light yellow. It is recommended that the diluted Defitelio solution be administered to patients using an infusion set equipped with a 0.2 µm in-line filter.

8. After the infusion is complete, the intravenous line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose 5% solution for infusion.

9. Administer Defitelio as described above. Do not co-administer other drugs through the same intravenous line.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 List of excipients
- Concomitant use of thrombolytic therapy (e.g. t-PA) (see section 4.5 Interactions with other medicines and other forms of interaction).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded in the patient file.

Haemorrhage

Use of medicines that increase the risk of haemorrhage within 24 hours of Defitelio administration (within 12 hours in the case of unfractionated heparin) is not recommended.

Concomitant systemic anticoagulant therapy (e.g. heparin, warfarin, direct thrombin inhibitors and direct factor Xa inhibitors) (see section 4.5 Interactions with other medicines and other forms of interaction), except for routine maintenance or reopening of central venous line, requires careful monitoring. Consideration should be given to discontinuation of Defitelio during use of such therapy.

Medicines that affect platelet aggregation (e.g. non–steroidal anti-inflammatory agents) should be administered with care, under close medical supervision, during Defitelio administration.

In patients who have or develop clinically significant acute bleeding requiring blood transfusion, Defitelio is not recommended or should be discontinued. Temporary discontinuation of Defitelio is recommended in patients who undergo surgery or invasive procedures at significant risk of major bleeding.

Hemodynamic Instability

Administration of defibrotide to patients who have haemodynamic instability, defined as inability to maintain mean arterial pressure with single pressor support, is not recommended.

Bolus administration

A bolus administration of Defitelio may cause flushing or a sensation of “generalised heat”. Bolus administration of Defitelio is not recommended.

This medicinal product contains 20.4 mg sodium per vial.

Use in the elderly

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.

Paediatric use

Defitelio is indicated for the use in adolescents, children and infants of 1 month of age and above (see section 4.8 Adverse effects (undesirable effects) – Paediatric population). The use of Defitelio in children aged less than one month is not recommended.

Effects on laboratory tests

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.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Potential interactions with recombinant t-PA

In a mouse model of thromboembolism, recombinant t-PA potentiated the antithrombotic effect of defibrotide when given intravenously and thus co-administration may present an increased risk of haemorrhage and is contraindicated (see section 4.3 Contraindications).

Potential interactions with antithrombotic fibrinolytic agents

Defibrotide has a profibrinolytic effect (see section 5.1 Pharmacodynamic properties – Mechanism of action) and this may potentially enhance the activity of antithrombotic/fibrinolytic medicinal products.

There is currently no reported experience in patients on the concomitant treatment with Low Molecular Weight Heparins (LMWHs), warfarin or the concomitant treatment with direct thrombin inhibitors (e.g., dabigatran etexilate) or direct Factor Xa inhibitors (e.g., rivaroxaban and apixaban). Therefore, the use of defibrotide with antithrombotic/fibrinolytic medicinal products is not recommended.

However, if used, in exceptional cases, caution should be exercised by closely monitoring the coagulation parameters (see section 4.4 Special warnings and precautions for use – Haemorrhage).

Potential interactions with other medicinal products

Defibrotide does not inhibit or induce CYP450s (see section 5.2 Pharmacokinetic properties – Metabolism).

4.6 FERTILITY, PREGNANCY AND LACTATION

Contraception in males and females

Effective contraception is required for patients and partners of patients during exposure to Defitelio and for one week subsequent to discontinuation.

Effects on fertility

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

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

Use in pregnancy

Category D

There are no studies using defibrotide in pregnant women. Embryo-fetal developmental toxicology studies in pregnant rats and rabbits of defibrotide doses close to the recommended therapeutic human dose, revealed a high rate of haemorrhagic abortion when infused intravenously over two hours at all dose levels tested. Due to this maternal toxicity, no conclusion can be drawn regarding the effects of defibrotide on embryo-fetal development. PAI-2 is known to be uniquely up-regulated in the placenta.

Defitelio should not be used during pregnancy unless the clinical condition of the woman requires treatment with Defitelio.

Use in lactation

It is not known whether defibrotide is excreted in human milk. Considering the nature of the medicinal product, a risk to the newborns/infants is not expected. Defitelio may be used during breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Defitelio has no or negligible influence on the ability to drive and operate machines. However, patients would not be expected to drive or operate machinery due to the nature of the underlying disease.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience

The safety assessment of Defitelio is based on pooled data from 176 subjects in the pivotal treatment study and the dose finding study. The overall incidence of adverse events was similar in the defibrotide treatment group and in the historical control group. The safety data from pooled data are supported and confirmed with data from the completed Treatment-IND study and postmarketing experience.

Table 1 describes adverse events that occurred at a rate of more than 5% in either the treatment group or the historical control group in the defibrotide 25 mg/kg/day pooled data.

Table 1: Treatment-Emergent Adverse Events Reported in > 5% of Subjects in Either the Pooled Data (defibrotide 25 mg/kg/day) or Historical Control in Patients with Severe VOD Post-HSCT

System Organ Class Preferred Term	**Defibrotide 25 mg/kg/day** **(N=176)**	**Historical Control** **(N=32)**
	Number (%) of patients	
At least 1 TEAE	169 (96.0)	32 (100.0)
Hypotension	65 (36.9)	16 (50.0)
Diarrhoea	43 (24.4)	12 (37.5)

Multi-organ failure	38 (21.6)	3 (9.4)
Veno-occlusive liver disease	32 (18.2)	2 (6.3)
Vomiting	31 (17.6)	8 (25.0)
Renal failure	29 (16.5)	1 (3.1)
Nausea	28 (15.9)	10 (31.3)
Epistaxis	24 (13.6)	5 (15.6)
Respiratory failure	20 (11.4)	4 (12.5)
Pyrexia	17 (9.7)	9 (28.1)
Hypertension	17 (9.7)	1 (3.1)
Hypoxia	17 (9.7)	0
Agitation	15 (8.5)	9 (28.1)
Haematuria	15 (8.5)	5 (15.6)
Pulmonary alveolar haemorrhage	15 (8.5)	5 (15.6)
Gastrointestinal haemorrhage	15 (8.5)	3 (9.4)
Confusional state	13 (7.4)	5 (15.6)
Peripheral oedema	13 (7.4)	4 (12.5)
Exfoliative rash	13 (7.4)	0
Pleural effusion	12 (6.8)	6 (18.8)
Sepsis	12 (6.8)	2 (6.3)
Abdominal pain	11 (6.3)	7 (21.9)
Conjunctival haemorrhage	11 (6.3)	3 (9.4)
Graft versus host disease	11 (6.3)	2 (6.3)
Decubitus ulcer	11 (6.3)	1 (3.1)
Sinus tachycardia	11 (6.3)	1 (3.1)
Tachycardia	10 (5.7)	14 (43.8)
Oedema	10 (5.7)	7 (21.9)
Bradycardia	10 (5.7)	6 (18.8)
Cough	10 (5.7)	3 (9.4)
Post procedural haemorrhage	10 (5.7)	1 (3.1)
Catheter site haemorrhage	10 (5.7)	0
Lung infiltration	10 (5.7)	0

Petechiae	9 (5.1)	9 (28.1)
Haematemesis	9 (5.1)	3 (9.4)
Mental status change	9 (5.1)	1 (3.1)
Pneumonia	9 (5.1)	1 (3.1)
Generalised oedema	8 (4.5)	8 (25.0)
Rash	8 (4.5)	7 (21.9)
Constipation	8 (4.5)	5 (15.6)
Anxiety	8 (4.5)	4 (12.5)
Blister	7 (4.0)	8 (25.0)
Graft versus host disease in skin	7 (4.0)	5 (15.6)
Hyperglycaemia	7 (4.0)	4 (12.5)
Convulsion	7 (4.0)	3 (9.4)
Chills	7 (4.0)	2 (6.3)
Back pain	6 (3.4)	3 (9.4)
Erythema	6 (3.4)	3 (9.4)
Pain	6 (3.4)	3 (9.4)
Pruritus	6 (3.4)	3 (9.4)
Tachypnoea	6 (3.4)	2 (6.3)
Hypothermia	5 (2.8)	5 (15.6)
Dyspnoea	4 (2.3)	5 (15.6)
Tremor	4 (2.3)	4 (12.5)
Bacteraemia	4 (2.3)	3 (9.4)
Mouth haemorrhage	4 (2.3)	3 (9.4)
Skin disorder	3 (1.7)	5 (15.6)
Insomnia	3 (1.7)	4 (12.5)
Bladder spasm	3 (1.7)	3 (9.4)
Hepatic failure	3 (1.7)	3 (9.4)
Capillary leak syndrome	3 (1.7)	2 (6.3)
Cardiac arrest	3 (1.7)	2 (6.3)
Contusion	3 (1.7)	2 (6.3)
Rash erythematous	3 (1.7)	2 (6.3)

Respiratory distress	3 (1.7)	2 (6.3)
Scrotal oedema	3 (1.7)	2 (6.3)
Septic shock	3 (1.7)	2 (6.3)
Alopecia	2 (1.1)	5 (15.6)
Coagulopathy	2 (1.1)	5 (15.6)
Lip haemorrhage	2 (1.1)	4 (12.5)
Face oedema	2 (1.1)	3 (9.4)
Acidosis	2 (1.1)	2 (6.3)
Cardiac failure congestive	2 (1.1)	2 (6.3)
Skin ulcer	2 (1.1)	2 (6.3)
Somnolence	2 (1.1)	2 (6.3)
Toxicity to various agents	2 (1.1)	2 (6.3)
Rales	1 (0.6)	6 (18.8)
Metabolic acidosis	1 (0.6)	4 (12.5)
Haematochezia	1 (0.6)	3 (9.4)
Atelectasis	1 (0.6)	2 (6.3)
Blood urine present	1 (0.6)	2 (6.3)
Graft versus host disease in intestine	1 (0.6)	2 (6.3)
Hypovolaemia	1 (0.6)	2 (6.3)
Irritability	1 (0.6)	2 (6.3)
Melaena	1 (0.6)	2 (6.3)
Periorbital haemorrhage	1 (0.6)	2 (6.3)
Pneumonia aspiration	1 (0.6)	2 (6.3)
Sinusitis	1 (0.6)	2 (6.3)
Skin exfoliation	1 (0.6)	2 (6.3)
Fluid overload	0	5 (15.6)
Disorientation	0	4 (12.5)
Graft versus host disease in liver	0	3 (9.4)
Jaundice	0	3 (9.4)
Nasal flaring	0	3 (9.4)
Gastrointestinal hypomotility	0	2 (6.3)

Haematocrit decreased	0	2 (6.3)
Hepatorenal syndrome	0	2 (6.3)
Incontinence	0	2 (6.3)

Adverse reactions of uncommon or lower frequency observed in pivotal treatment study and dose-finding study are listed below, by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

List of adverse reactions of uncommon or lower frequencies in the pivotal treatment study and the dose-finding study (25 mg/kg/day) pooled data:

Gastrointestinal disorders:
Uncommon: Haematemesis; Upper gastrointestinal haemorrhage; Gastric haemorrhage; Haematochezia; Melaena; Mouth haemorrhage
General disorders and administration site conditions
Uncommon: Chills; Feeling hot; Puncture site haemorrhage
Investigations
Uncommon: International normalised ratio increased
Nervous system disorders
Uncommon: Lethargy; Spinal haematoma; Subarachnoid haemorrhage; Subdural hygroma
Reproductive system and breast disorders
Uncommon: Menorrhagia
Respiratory, thoracic and mediastinal disorders
Uncommon: Haemothorax; Thoracic haemorrhage
Skin and subcutaneous tissue disorders
Uncommon: Dry skin; Pruritus generalised; Purpura; Skin haemorrhage
Vascular disorders
Uncommon: Flushing; Haemorrhage; Haematoma

Postmarketing Experience

In addition to adverse reactions from clinical studies, the following adverse reactions were identified during post-approval use of products containing defibrotide.

Immune system disorders
Uncommon: Anaphylactic reaction, Hypersensitivity

Paediatric population

In the treatment studies over 50% of the patients were children. In doses above the recommended dose of 25 mg/kg/day there was a higher proportion of patients with bleeding events in the high dose group but since many events occurred in the follow-up period, a clear relationship with defibrotide treatment could not be determined.

A small numerical increased incidence of fatal haemorrhagic events has been observed in paediatric subjects exposed to defibrotide at doses of 25 mg/kg/day or higher, compared to historical controls. In this treatment group, causality was difficult to determine given multiple comorbidities.

The frequency nature and severity of adverse reactions in children are otherwise the same as in adults. No special precautions are indicated.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via -local reporting system.

4.9 OVERDOSE

There is no specific antidote for overdose and treatment should be symptomatic. Defibrotide is not removed by dialysis (see section 5.2 Pharmacokinetic properties – Special populations – Renal impairment).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: other antithrombotic agents; ATC code: B01AX01.

Mechanism of action

Defibrotide is an oligonucleotide mixture with demonstrated antithrombotic, fibrinolytic, anti-adhesive and anti-inflammatory actions. The mechanism of action is multifactorial. It primarily acts through reducing excessive endothelial cell (EC) activation (endothelial dysfunction), thereby modulating endothelial homeostasis and maintaining the thrombo-fibrinolytic balance. However, the exact mechanism of action of defibrotide is not fully elucidated.

Defibrotide has demonstrated antithrombotic and fibrinolytic effects *in vitro* and *in vivo* by: increasing systemic tissue factor pathway inhibitor (TFPI), tissue plasminogen activator (t-PA) and thrombomodulin (TM) expression; decreasing von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1) expression; and enhancing the enzymatic activity of plasmin to hydrolyse fibrin clots.

In vitro and *in vivo* studies have demonstrated that defibrotide inhibits leukocyte and platelet adhesion to endothelium by: suppressing P-selectin and vascular cell adhesion molecule-1 (VCAM)-1; interfering with lymphocyte function-associated antigen 1-intercell adhesion molecule (LFA-1-ICAM) mediated leukocyte transmigration; and increasing nitric oxide (NO), Prostaglandin I2 (PGI2) and Prostaglandin E2 (PGE2).

In vitro defibrotide demonstrates anti-inflammatory effects that attenuates the release and production of reactive oxygen species and inflammatory mediators such as interleukin 6, thromboxane A2, leukotriene B4 and tumour necrosis factor-α (TNF-α).

In vitro and *in vivo* studies have shown that defibrotide protects ECs from damage and promotes tissue homeostasis by decreasing fludarabine-mediated apoptosis of EC while maintaining its anti-leukemic effect and by inhibiting the expression of heparanase.

Clinical trials

The efficacy and safety of defibrotide in the treatment of severe VOD were studied in a pivotal Phase 3 historical-controlled study (2005-01). Forty-four children and 58 adult patients with severe VOD post-HSCT, were treated with Defitelio 25 mg/kg/day by intravenous infusion, and compared with 32 historical control patients. Median length of therapy in those treated with Defitelio was 22 days.

Day+100 survival rate was improved in the Defitelio group with 38.2% (39/102) of the patients surviving versus 25.0% (8/32) in the historical control group (p=0.0109). In addition, a significantly higher proportion of patients in the Defitelio treated group achieved a complete response, defined as total bilirubin less than 2 mg/dL and resolution of MOF (multiple organ failure); Day+100 complete response was 25.5% (26/102) with Defitelio versus 12.5% (4/32) in the historical control (p=0.016).

The efficacy data from this pivotal study are supported and confirmed with data from a dose-finding study (25 mg/kg arm) and the Open Label Treatment-IND study, as presented in Table 2.

Table 2: Treatment Study Results: Complete Response and Survival Rate of Severe VOD at Day+100

<table>
<tr><th></th><th colspan="2">Historically Controlled Trial
(25 mg/kg/day)</th><th colspan="2">Individual Studies</th></tr>
<tr><th></th><th>Defibrotide treated group N=102</th><th>Historical Control N=32</th><th>Dose-Finding (25 mg/kg/day arm) N=75</th><th>Open Label Treatment IND (25 mg/kg/day) N=512</th></tr>
<tr><td rowspan="2">Survival by Day+100</td><td>38.2%*</td><td>25.0%*</td><td rowspan="2">44.0%*</td><td rowspan="2">48.2%*</td></tr>
<tr><td colspan="2">p=0.0109</td></tr>
<tr><td rowspan="2">Complete Response by Day+100</td><td>25.5%</td><td>12.5%</td><td rowspan="2">46.7%</td><td rowspan="2">39.3%</td></tr>
<tr><td colspan="2">p= 0.0160</td></tr>
</table>

*=Kaplan Meier estimates for time-to-event analysis by Day100

Outcome data available from 701 patients treated with Defitelio for VOD post-transplant in an international, open label, compassionate use program are consistent with the controlled clinical trial, with a Kaplan-Meier estimated survival at Day+100 of 57.6% in patients with VOD receiving defibrotide doses of 25 mg/kg/day.

Return of outcome data for this program was not mandated and was highly variable compared to formally conducted clinical trials.

Data derived from an independent US registry have shown a beneficial effect of Defitelio in routine clinical practice. At an interim analysis of the on-going registry, data from 96 patients with severe VOD were available.

The Day+100 all-cause mortality in patients with severe VOD who were not treated with defibrotide was 69%, and 61% in those patients who received defibrotide. These data are from an open label registry with subjects not randomised and data on dose or duration of defibrotide treatment were not collected.

Additional information is shown in the following Table 3.

Table 3: US Registry data

	Non-defibrotide treated N=55	**Defibrotide treated N=41**
Alive at Day +100	17 (31%)	16 (39%)
VOD resolved by Day +100	16 (29%)	21 (51%)

Paediatric population

In each of the clinical trials performed in the treatment of VOD, over 50% of patients were under the age of 18 years. Safety information in children is also available from a prevention study conducted solely in children. Safety and efficacy in children aged less than 1 month have not yet been established.

Cardiac electrophysiology

Based on the results of the QTc study, conducted in healthy subjects at therapeutic and supra-therapeutic doses, it can be concluded that Defitelio has no significant or clinically relevant QTc-prolonging potential at doses up to 2.4 times higher than therapeutically indicated. Defitelio might be considered free of proarrhythmic toxicity related to QT changes.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and Distribution

Defibrotide PK parameters from patients (N=10) with severe VOD receiving 6.25 mg/kg dose and participating in PK sub-study in the dose finding study (99-118) are presented in Table 4.

Table 4. Defitelio pharmacokinetic parameters of patients with severe VOD following HSCT, receiving a dose of 6.25 mg/kg

Parameter	**Defitelio PK parameters Mean**
Kel (1/min)	0.0082[#]
T½ (min)	102[#]
Tmax (min)	123.5
Cmax (µg/mL)	47.3
AUC (min-µg/mL)	5602.8
Cl (mL/min)	58.2[#]
Vdss (mL)	8080.2[#]

N=9

Maximum plasma concentrations peak at the end of the infusion period and decline thereafter with a rapid clearance. Defitelio is undetectable in most samples by 3.5 hours after the start of the infusion.

Pharmacokinetic modelling simulation analysis show that Defitelio plasma concentrations do not accumulate upon multiple dose administration and with doses up to 4-fold the therapeutic dose.

Volume of distribution is around 8.1 to 9.1 L.

In vitro studies demonstrate that 93% of Defitelio is bound to plasma proteins.

Metabolism

Defibrotide does not inhibit or induce CYP450s.

Excretion

Metabolism followed by urinary excretion is likely the main route of elimination. The estimated total clearance is 3.4 to 6.1 L/h.

After administration of the therapeutic dose (6.25 mg/kg) to healthy subjects, an average of 9.48% of the total dose administered is excreted in urine as unchanged defibrotide in 24 hours, with the majority excreted during the first collection interval of 0-4 hours (approximately 98%).

Special populations

Renal impairment

Six patients with an estimated glomerular filtration rate <30 mL/min/1.73m^2 (calculated using the Modification of Diet in Renal Disease equation) and not currently on dialysis were compared to 6 healthy subjects with similar baseline demographics. Defitelio 6.25 mg/kg was administered intravenously over 2 hours to subjects every 6 hours. Compared to healthy controls, subjects with renal impairment demonstrated 1.6– and 1.4-fold increases in AUC and Cmax, respectively and a half-life of about twice that of healthy subjects.

The amount of defibrotide excreted in urine over 24 hrs was about 5% of the total dose administered in those with renal impairment versus about 12% in healthy subjects.

Almost all renal excretion occurs within the first 4 hours. Accumulation of defibrotide over 4 doses was not found. Difference in exposure is not considered clinically relevant and so dose adjustment is not advised for patients with renal impairment (see section 4.2 Dose and method of administration – Renal impairment).

In a sub-study it was shown that haemodialysis did not remove defibrotide (see section 4.2 Dose and method of administration – Renal impairment)

Hepatic impairment

No formal pharmacokinetic studies have been performed in hepatic impaired patients. Defitelio has been used in clinical trials in patients with hepatic impairment without dose adjustment with no major safety issues identified (see section 4.2 Dose and method of administration – Hepatic impairment).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity.

Carcinogenicity

While there was no evidence of carcinogenic potential following 2 years of dietary defibrotide administration to mice and rats (at up to 2000 mg/kg/day), this is not the clinical route of administration and the relative defibrotide exposure would be substantially less compared to intravenous administration, allowing limited conclusions to be drawn from these studies.

Juvenile toxicity

Repeated intravenous administration of defibrotide, at doses below and close to the human therapeutic dose, to juvenile rats resulted in a delay in the mean age of preputial separation, suggesting a delay in the onset of male puberty in rats. However, the clinical relevance of these findings is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium citrate dihydrate

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injections

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2 Dose and method of administration – Method of administration.

6.3 SHELF LIFE

Unopened vials

3 years.

In-use stability after first opening and/or dilution

From a microbiological point of view, after dilution, the reconstituted medicinal product should be used immediately.

If not used immediately, store at 2-8°C and discard after 24 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not freeze.

For storage conditions after dilution of the medicinal product, see section 6.3 Shelf life.

6.5 NATURE AND CONTENTS OF CONTAINER

2.5 mL vials (Type I clear glass), closed with a stopper (butyl rubber) and seal (aluminium).

Pack size of 10 vials.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Defitelio is for single use in one patient only. Discard any unused contents.

Any unused medicinal product or waste material should be disposed of in accordancewith local requirements.

7. MARKETING AUTHORISATION HOLDER

Link Healthcare Hong Kong Limited
Unit 16, Floor 12
Corporation Square
8 Lam Lok Street
Kowloon Bay
Hong Kong

8. DATE OF APPROVAL BY HONG KONG DEPARTMENT OF HEALTH

30 September 2026