SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Defitelio® 80 mg/ml concentrate for solution for infusion

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, and corresponding to a concentration in the range of 4 mg/ml to 20 mg/ml after dilution.
* produced from porcine intestinal mucosa.

Excipient with known effect
Each vial contains 0.89 mmol (equivalent to 20.4 mg) sodium.

For the full list of excipients, see section 6.1.

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 indication

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 over 1 month of age.

4.2 Posology 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.

Posology

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.

Renal impairment

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

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).

Paediatric population

The recommended dose for children aged 1 month 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 has 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, to a suitable concentration to permit infusion over 2 hours. The total volume of infusion should be determined based on the individual's patient 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)

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
Concomitant use of thrombolytic therapy (e.g. t-PA) (see section 4.5).

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.

Use of medicinal products 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), 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.

Medicinal products 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.

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

A bolus administration of Defitelio® may cause flushing or a sensation of "generalised heat".

This medicinal product contains 20.4 mg sodium per vial, equivalent to 1.02% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products 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).

Potential interactions with antithrombotic fibrinolytic agents

Defibrotide has a profibrinolytic effect (see section 5.1) 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) 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).

Potential interactions with other medicinal products

Defibrotide does not inhibit or induce CYP450s (see section 5.2).

4.6 Fertility, pregnancy and lactation

<u>Contraception in males and females</u>

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

Pregnancy

There are no studies using defibrotide in pregnant women. Embryo-foetal 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 (see section 5.3).

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

Breast-feeding

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.

Fertility

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

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 Undesirable effects

Summary of the Safety Profile

The safety evaluation of defibrotide is based on the safety pooled data set, which included patients who received 25 mg/kg of defibrotide for the treatment of VOD, from 4 clinical studies: The Phase 3 pivotal treatment study (2005-01), the Treatment-IND study, the dose-finding study (99-118), and a controlled randomised prophylaxis study (2004-000592-33)In the Phase 3 pivotal treatment study ,the overall incidence of adverse events was similar in the defibrotide treatment group and in the control group (historical). The tabulated list of adverse reactions incorporates the ADRs observed in the safety pooled data set [ADR = any event reported as possibly related on at least two occasions] and TEAEs observed in the final completed Treatment-IND 2006-05 study [TEAE = any AE that started or worsened in severity after the first dose of defibrotide]. For the adverse reactions reported the highest frequency was used in the table below. The safety data from the pivotal study are supported and confirmed with data from the completed Treatment-IND study.

The most frequent adverse reactions observed during the treatment of hepatic VOD are haemorrhage (including but not limited to gastrointestinal haemorrhage, pulmonary haemorrhage and epistaxis) and hypotension.

In addition, although in the defibrotide studies in VOD there have been no reports of hypersensitivity, cases of hypersensitivity including anaphylaxis were reported from a previously marketed formulation of defibrotide, consequently hypersensitivity is included as an ADR.

Tabulated list of adverse reactions

Adverse reactions observed are listed below, by system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. 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).

Blood and lymphatic system disorders	
Common	Coagulopathy
Immune system disorders	
Uncommon	Hypersensitivity
	Anaphylactic reaction
Nervous system disorders	
Common	Cerebral haemorrhage
Uncommon	Cerebral haematoma
Eye disorders	
Uncommon	Conjunctival haemorrhage
Vascular disorders	
Very common	Hypotension
Common	Haemorrhage
Respiratory, thoracic and mediastinal disorders	
Common	Pulmonary haemorrhage
	Epistaxis
Uncommon	Haemothorax
Gastrointestinal disorders:	
Common	Gastrointestinal haemorrhage
	Vomiting
	Diarrhoea
	Nausea
	Haematemesis
	Mouth haemorrhage
Uncommon	Melaena
Skin and subcutaneous tissue disorders	
Common	Rash
	Pruritus
	Petechiae
Uncommon	Ecchymosis
Renal and urinary disorders	
Common	Haematuria
General disorders and administration site conditions	
Common	Catheter site haemorrhage
	Pyrexia
Uncommon	Injection site haemorrhage

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. In the paediatric prevention

study at 25 mg/kg/day there was an increased incidence of any bleeding events in the defibrotide group compared with the treatment group.

However there was no difference in incidence of serious bleeding or bleeding events with fatal outcome.

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

Reporting of 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.
To report any side effect(s):

The National Pharmacovigilance Centre (NPC):
SFDA Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

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).

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), modulating endothelial homeostasis as well as restoring 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 attenuate 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).

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, shown in *in vitro* and *in vivo* studies respectively.

Clinical efficacy and safety

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 intravenous by infusion, and compared with 32 historical control patients. Median length of therapy in those treated with Defitelio® was 22 days.

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 23.5% (24/102) with Defitelio® versus 9.4% (3/32) in the historical control (p=0.013). In addition, 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=0.034). 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 Tables 1.

Table 1: Treatment Study Results: Complete Response and Survival Rate of Severe VOD at Day+100

	Individual Studies			
	Dose-Finding (25mg/kg/day arm)	**Open Label Treatment IND (25mg/kg/day)**	**Historically Controlled Trial (25mg/kg/day)**	
			Defibrotide treated group	**Historical Control**
Complete Response by Day+100	43% (32/75)	39.3% (201/512)	23.5% (24/102)	9.4% (3/32)
			p= 0.0131	
Survival by Day+100	43.9%*	49.5%*	38.2%*	25.0%*
			p=0.0341	

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

Outcome data available from 611 patients treated with Defitelio® on a compassionate use basis for non-severe and severe VOD post-transplant, are consistent with the controlled clinical trials, with complete response rate 24% (51/212) and survival 37% (78/212) in the subset of patients with severe VOD.

A controlled randomised prophylaxis study (Study 2004-000592-33) was conducted in the paediatric patients undergoing HSCT. Patients (n=356) were randomised to receive 25 mg/kg/day from the start of conditioning or were randomised to receive no prophylaxis.

A 40% reduction in the overall incidence of VOD in the Defitelio® prophylaxis arm (from 19.9% in the control arm to 12.2% in the Defitelio® arm), has been shown. The use of Defitelio® rescue treatment for all patients who developed VOD meant that the study was not designed to assess any survival advantage and none was seen in this study.

In secondary analyses on the subset of patients undergoing allogeneic transplants, Defitelio® prophylaxis was also associated with a lower incidence and less Grade 2 to 4 severity of acute graft versus host disease (aGvHD) by Day+100.

Coppell *et al* in 2010 reported data from a large meta-analysis of 235 patients with severe VOD showing a background mortality rate of severe VOD of 84.3% and that this mortality rate has remained constant over several decades.

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 and the subjects were not randomised.

Additional information is shown in the following Table 2.

Table 2: US Registry data

	Non-defibrotide treated	**Defibrotide treated**
	55	**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 are available from the 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

In 52 healthy volunteers, after a single 6.25 mg/kg dose of Defitelio® given as a 2-hour infusion, the pharmacokinetic parameters were as follows:

Table 3. Defitelio® pharmacokinetic parameters after intravenous infusion of 6.25 mg/kg to healthy subjects.

Parameter	Defitelio® PK Parameters Mean ± SD
C_{max} (µg/ml)	17.3 ± 3.83
t_{max} (h)#	2.00 (1.00-2.00)

AUCt (µg/ml*h)	26.9 ± 8.53
AUC (µg/ml*h)	48.1 ± 6.49
Vd (ml)	9934 ± 3807
CL (L/h)	10.4 ± 1.77
Kel (1/h)	1.25 ± 0.66
$t_{1/2}$ (h)	0.71 ± 0.35

median (min-max)

Maximum plasma concentrations peaked at the end of the infusion period and declined thereafter with a rapid clearance and most of samples were undetectable 3.5 hours after the start of the infusion.
Pharmacokinetic modelling simulation analysis showed 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 10 L. *In vitro* studies demonstrate that 93% of Defitelio® is bound to plasma proteins.

Elimination

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%).

Metabolism

Defibrotide does not inhibit or induce CYP450s.

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).

In a sub-study it was shown that haemodialysis did not remove defibrotide (see section 4.2)

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).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity.

In both species, the main findings were accumulation of vacuolated macrophages in liver of dogs and in liver, kidneys and lymph nodes of rats. Macrophages are considered the main target organ.

Embryo-foetal development

In the Segment II reproductive studies in rats and rabbits, defibrotide has shown maternal toxicity by inducing a high rate of haemorrhagic abortion when infused intravenously over two hours at all dose levels tested including doses close to the human dose. Due to this maternal toxicity, no conclusion can be drawn regarding the effects of defibrotide on embryo-foetal development. PAI-2 is known to be uniquely up-regulated in the placenta.

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

Amounts per a vial
Sodium citrate, dihydrate – 25.0 mg
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections – 2.5 ml

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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. However, chemical and physical in-use stability has been demonstrated for 72 hours at 15-25°C for a concentration range of 4 mg/ml to 20 mg/ml in sodium chloride 9 mg/ml (0.9%) solution for infusion or 5% glucose solution for infusion.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be expected to exceed 24 hours at 2-8°C.

6.4 Special precautions for storage

Store below 25ºC. Do not freeze.

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

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 and other handling

Defitelio® is for single use only.

The concentrate solution for infusion has to be diluted using aseptic technique.

Defitelio® should be diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion or 5% glucose solution for infusion (see section 6.3 for concentration range and stability of the diluted solution) to a suitable concentration to permit 2 hours infusion time (see section 4.2).

Preparation of Defitelio® (use aseptic technique):

1. The number of vials to be diluted should be determined based on the individual patient's weight (see section 4.2).
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 total volume of infusion 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).
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 should be withdrawn and discarded, equal to the total volume of Defitelio® solution to be added.
5. The required volume from the Defitelio® vials should be withdrawn and combined.
6. 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.
7. The solution for infusion should be mixed gently.
8. 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.
9. 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.

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

7. MARKETING AUTHORISATION HOLDER

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