Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Defibrotide

Proprietary Product Name: Defitelio

Sponsor: Link Medical Products Pty Ltd

December 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ALT	Alanine aminotransferase
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AusPAR	Australian Public Assessment Report
BMI	Body mass index
BSA	Body surface area
CHMP	Committee for Medicinal Products for Human Use (European Union)
CI	Confidence interval
CIBMTR	Centre for International Blood and Marrow Transplant Research
CMI	Consumer Medicine Information
CPD	Certified Product Details
CR	Complete response
DF-CUP	Defitelio - compassionate use program
DLP	Data lock point
EMA	European Medicines Agency (European Union)
ESDR	End stage renal disease
EU	European Union
FDA	Food and Drug Administration (United States of America)
GvHD	Graft versus host disease
HC	Historical control
HSCT	Haematopoietic stem-cell transplantation

Abbreviation	Meaning
IM	Intramuscularly
IPC	In process control
ITT	Intent/intention to treat
IV	Intravenous
LMWH	Low molecular weight heparin
MOD	Multiple organ dysfunction
MOF	Multiple organ failure
MRC	Medical review committee
MW	Molecular weight
PAI-1	Plasminogen activator inhibitor 1
PD	Pharmacodynamics(s)
PI	Product Information
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetic(s)
PSUR	Periodic safety update report
q6h	Every 6 hours
RCT	Randomised controlled trial
RMP	Risk management plan
RUQ	Right upper quadrant
SAS	Special Access Scheme
SOC	System Organ Class
SOS	Sinusoidal obstruction syndrome
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
tPA	Tissue plasminogen activator
US(A)	United States (of America)

Abbreviation	Meaning
VOD	Veno-occlusive disease

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Product name:	Defitelio
Active ingredient:	Defibrotide
Decision:	Approved
Date of decision:	15 July 2020
Date of entry onto ARTG:	23 July 2020
ARTG number:	319221
▼ *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	Link Medical Products Pty Ltd PO Box 718 Mona Vale, NSW 1660
Dose form:	Concentrated solution for infusion (sterile concentrate)
Strength:	200 mg/2.5 mL
Container:	Vial
Pack size:	10
Approved therapeutic use:	*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
Route of administration:	Intravenous (IV)
Dosage:	Defitelio must be prescribed and administered to patients by specialised physicians experienced in the diagnosis and

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

	treatment of complications of haematopoietic stem cell transplantation (HSCT). 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 veno-occlusive disease (VOD) resolve. For further information regarding dosage, refer to the Product Information (PI).
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Link Medical Products Pty Ltd (the sponsor) to register Defitelio (defibrotide) 200 mg/2.5 mL, concentrated solution for the following proposed 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 of 1 month of age and above.*

Hepatic veno-occlusive disease (VOD), now more commonly referred to as hepatic sinusoidal obstruction syndrome (SOS), is a rare and life threatening complication of haematopoietic stem cell transplant (HSCT), commonly referred to as a 'bone marrow' transplant, which usually develops in the early post-transplant period, and occurs in about 3% of patients after autologous HSCT and up to 60% of patients after allogeneic HSCT.[2] The clinical syndrome comprises rapid weight gain, fluid retention with ascites, painful hepatomegaly and jaundice. Severe hepatic VOD is accompanied by multiple organ dysfunction or failure (MOD/MOF) affecting the respiratory, renal and central nervous (hepatic encephalopathy) systems as well as the liver. If left untreated, severe VOD is associated with a mortality rate greater than 80%. The condition is thought to occur owing

[2] In **autologous HSCT**, the transplant involves taking stem cells the same person who will get the transplant making the patient their own donor. so the patient is their own donor. In **allogeneic HSCT**, stem cells are taken from another closely matched related or unrelated donor.

to damage, activation, death and detachment of endothelial cells within the liver sinusoids, ultimately resulting in the deposition of fibrin clots within the sinusoids. This endothelial cell activation and damage is thought to be initially triggered by the chemotherapy and radiotherapy included in the HSCT conditioning regimens. Later insults to the endothelial cells include exposure to the cytokines produced by the injured tissues, endogenous microbial products translocated through damaged mucosal barriers, drugs used during the HSCT procedure, and the process of engraftment itself. Factors that are thought to predispose to VOD include pre-existing liver disease, and younger patient age.

There are no approved therapies specific to hepatic VOD available in Australia. Patients are treated with sodium and fluid restrictions and diuretics and if the condition progresses, with dopamine, sodium heparin, low molecular weight heparin (LMWH), or recombinant tissue plasminogen activator (tPA) depending on the severity. While heparin has been approved for prophylaxis and treatment of thromboembolic disorders such as thrombophlebitis, pulmonary embolism, coronary or venous thrombosis and occlusive vascular disease, it is not approved for hepatic veno-occlusive disease. The use of tPA is generally not recommended because of an associated risk of haemorrhage.

Defitelio (defibrotide) is considered a 'first in class' medicine for VOD, and has been supplied in Australia for VOD and VOD prophylaxis under the Special Access Scheme (SAS) since November 2010.[3]

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this application, similar applications had been approved in European Union (EU) (18 October 2013), Israel (12 May 2015), South Korea (19 February 2016), United States of America (USA) (30 March 2016), Canada (10 July 2017), Brazil (11 March 2019) and Japan (18 June 2019).

[3] The **Special Access Scheme** (**SAS**) allows certain health practitioners to access therapeutic goods (such as medicines, medical devices or biologicals) that are not included in the Australian Register of Therapeutic Goods (ARTG) for a single patient. Therapeutic goods that are not included in the ARTG (and are not otherwise exempt from being in the ARTG) are described by the TGA as 'unapproved'.

Table 1: International regulatory status for Defitelio

Region	Submission date	Status	Approved indications
European Union	3 May 2011	Approved on 18 October 2013	*Defitelio is indicated for the treatment of severe hepatic venoocclusive 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.*
Israel	28 July 2014	Approved on 12 May 2015	*Defitelio is indicated for the treatment of severe hepatic venoocclusive 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.*
South Korea	29 June 2015	Approved on 19 February 2016	*Treatment of severe hepatic veno occlusive disease (VOD) in haematopoietic stem-cell*

Region	Submission date	Status	Approved indications
			transplantation (HSCT) therapy.
United States of America	31 July 2015	Approved on 30 March 2016	*Defitelio 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).*
Canada	29 November 2016	Approved on 10 July 2017	*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.*
Brazil	17 November 2017	Approved on 11 March 2019	*Defitelio (defibrotide) solution for dilution for*

Region	Submission date	Status	Approved indications
			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
Japan	11 October 2018	Approved 18 June 2019	*Hepatic sinusoidal obstruction syndrome (hepatic veno-occulsive disease).*
Switzerland	31 July 2019	Under consideration	*Under consideration*

Product Information

The PI approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2019-01763-1-3

Description	Date
Designation Orphan;[4]	21 February 2019
Submission dossier accepted and first round evaluation commenced	31 July 2019
First round evaluation completed	4 February 2020
Sponsor provides responses on questions raised in first round evaluation	21 February 2020
Second round evaluation completed	22 May 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	12 May 2020
Sponsor's pre-Advisory Committee response	26 May 2020
Advisory Committee meeting	June 2020
Registration decision (Outcome)	15 July 2020
Completion of administrative activities and registration on the ARTG	23 July 2020
Number of working days from submission dossier acceptance to registration decision*	223

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

[4] **Orphan designation**: 'Orphan drugs' are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related orphan designation is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

The TGA has adopted the following guidance documents relevant to this submission:

- Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population. CPMP/ICH/2711/99; EU/ICH effective date: 19 April 2001.
- Guideline on pharmaceutical development of medicines for paediatric use A/CHMP/QWP/805880/2012 Rev. 2.; EU/ICH effective date: 15 September 2014.
- Guideline on the role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population EMEA/CHMP/EWP/147013/2004 Corr.; EU/ICH effective date: 24 August 2009.
- Points to consider on Applications with 1. Meta-analyses; 2. One Pivotal Study. CPMP/EWP/2330/99; effective date: 31 May 2001.

Quality

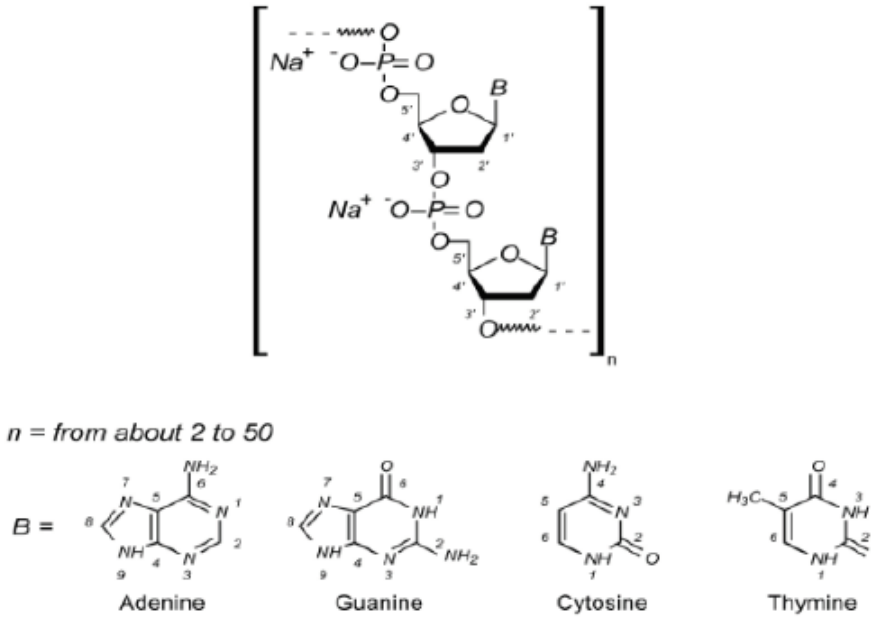
The quality evaluator has no objections to the registration of defibrotide for the proposed indication.

Defibrotide is an oligonucleotide mixture derived from porcine intestinal mucosa comprised predominantly of single stranded polydeoxyribonucleotides of varying lengths (described as 'polydisperse'). The chemical name of defibrotide is polydeoxyribonucleotide, sodium salt.

Defibrotide is prepared by controlled depolymerisation of DNA isolated from the mucosa, applying a specific and validated combination of physico-chemical conditions. The individual oligonucleotides that comprise defibrotide differ with respect to length, sequence, and inter- or intra strand hybridisation. Due to the large number of individual components of different lengths and sequences, defibrotide cannot be said to have a single discrete structure. However, information can be obtained with respect to the average molecular weight (MW) of the oligonucleotide components of defibrotide.

The chemical structure of defibrotide is shown in Figure 1.

Figure 1: Chemical structure of defibrotide



The specific important manufacturing aspects for this product are accurate characterisation of the polydisperse mixture, and application of in-process controls (IPC)

that ensure purity (including the absence of adventitious agents and contaminants), and confirm biological activity.

All manufacturing steps and analytical procedures have been validated.

Proposed conditions of registration

The quality evaluator recommends the following conditions of registration:

Batch Release Testing & Compliance with Certified Product Details

It is a condition of registration that all batches of Defitelio (defibrotide) imported into Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

It is a condition of registration that up to five initial batches of Defitelio (defibrotide) imported into Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index.

The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at https://www.tga.gov.au/publication/testing-biological-medicines.

This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until sponsors are notified in writing of any variation.[5]

Certified Product Details

The CPD, as described in *Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM)* (http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change. CPDs should be emailed to Biochemistry.Testing@health.gov.au as a single PDF document.

Nonclinical

The nonclinical evaluator has no objections to the registration of defibrotide for the proposed indication.

Although the mechanism of action of defibrotide has not been fully elucidated, the sponsor proposes that the mechanism of action is through stabilisation and protection of the intrahepatic endothelial cells. Primary pharmacological evidence from sponsor conducted

[5] TGA updated batch release testing conditions of approval,
Laboratory testing & compliance with Certified Product Details (CPD)
i. All batches of ***Defitelio(defibrotide) 200 mg/2.5 mL concentrated solution for infusion vial*** *supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).*
ii. When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs index and periodically in testing reports on the TGA website.

studies plus published *in vivo*, *ex vivo* and *in vitro* studies showed that defibrotide has complex effects, promoting the thrombo-fibrinolytic balance and providing anti-inflammatory protection. No standalone secondary pharmacodynamics (PD) studies were conducted. Safety pharmacology measurements of central nervous, cardiovascular and respiratory systems were integrated into repeat dose toxicity studies and did not indicate any significant risk of defibrotide to the major vital organ systems.

Based on the *in vitro* studies, defibrotide does not inhibit or induce common drug metabolising enzymes and is not a substrate or inhibitor of a number of common human uptake transporters or efflux transporters. Clinically relevant pharmacokinetic (PK) drug-drug interactions are considered unlikely. Pivotal repeat dose toxicity studies were conducted in rats exposed to 24 hours continuous IV infusions and in dogs receiving 2 hours infusion of defibrotide four times per day at relative exposure levels up to 35 to 40 fold the clinical dose of defibrotide (based on body surface area, (BSA)). Results from the rat study were inconclusive due to high mortality related to catheter complications, which were not directly defibrotide related. In dogs, there was an increase in liver weight and some microscopic findings of uncertain toxicological significance (minimal to mild Kupffer cell hypertrophy, minimal subacute inflammation, mild individual hepatocellular necrosis). It was suggested that the changes are probably caused by cellular uptake of defibrotide.

Defibrotide was not mutagenic in a bacterial mutation assay or clastogenic *in vitro* or *in vivo*. Two year carcinogenicity studies in rats and mice fed with defibrotide showed no treatment related increases in tumour incidence but the actual relative plasma exposure achieved with oral administration is likely to be well under that attained using the IV route in a clinical setting.

Defibrotide injected intramuscularly (IM) at doses of up to 12 mg/kg/day showed no significant treatment related effects in rat studies of fertility or early embryonic development and peri-postnatal development. However, the relative exposure levels from IM injections are likely to be well under those anticipated clinically with IV infusion. Embryofetal development studies in which pregnant rats and rabbits received continuous IV infusion of defibrotide revealed severe maternotoxicity (a high rate of haemorrhagic abortion), which interfered with adequate assessment of effects on embryofetal development. A follow up study in rabbits at 80 mg/kg defibrotide (corresponding to a BSA-adjusted daily dose similar to that in humans) using staggered 5 days treatment windows reported no maternotoxicity or adverse effects on embryofetal development. The sponsor has proposed Pregnancy Category D.[6] This category is appropriate in view of the findings of the embryofetal developmental toxicology studies.

The main finding in a juvenile rat study (IV defibrotide bolus at doses of up to 320 mg/kg/day for 28 days) was a delay in the mean age of the occurrence of preputial separation, suggesting a delay in the onset of male puberty. This finding was not reproduced in a follow up study but is still noted in the draft PI.

Defibrotide did not cause any apparent allergic, immunogenic or immunotoxic responses in animal studies.

[6] **Pregnancy Category D**: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Clinical

Content of the clinical dossier

The clinical dossier consists of:

- eight pharmacology studies;
- one population pharmacokinetic (popPK) analysis;
- one main efficacy and safety study (Study 2005-01);
- six supporting efficacy/safety studies; and
- ten periodic safety update reports (PSURs).

Pharmacology

Pharmacokinetics

Defibrotide is administered over two hours by IV infusion and the peak plasma concentration occurs at the end of each infusion. Defibrotide is highly protein bound, has a small volume of distribution and a short plasma half-life, with 10 to 14% of the dose excreted in urine as polydeoxyribonucleotides. Defibrotide administered every six hours (q6h) does not appear to accumulate in the short term. Haemodialysis did not remove defibrotide and did not appear to have a noticeable effect on the plasma clearance of defibrotide.

Population pharmacokinetic data

A population pharmacokinetic (popPK) model (GENT-PCS-103) was developed to assess sources of variability in PK parameters and to predict defibrotide exposure in paediatric patients with VOD. The model included data for 83 subjects (58 healthy volunteers, 6 volunteers with end stage renal disease (ESRD) on dialysis and 6 volunteers with severe or ESRD not on dialysis, and thirteen study participants with VOD, of which two were under the age of 16). Overall, the final model for defibrotide PK was a one compartment model with linear elimination.

The PK evaluator identified two major weaknesses with the popPK model. First, in the opinion of the evaluator the complexity of the clinical picture of VOD, inherent hepatic impairment and renal impairment was not captured well in the modelling process. This was indicated by a disproportionate decrease (up to 4 folds) in defibrotide renal clearance with renal impairment when urinary excretion only accounted for up to 15% of total excretion. In paediatric simulations, PK parameters were not significantly changed by removing creatinine clearance as a covariate from the model. The use of alanine aminotransferase (ALT) to represent hepatic impairment was queried. The second concern was that the analysis only included data from two paediatric patients. The evaluator suggested that the model would be more relevant if more paediatric data had been included, given the frequency of VOD in the paediatric population. In view of the identified weaknesses, the evaluator concluded that the model described the data well, but its utility was uncertain.

Pharmacodynamics

The clinical studies demonstrated that defibrotide had no effect on cardiac parameters, did not affect coagulation parameters in healthy volunteers nor did it affect haemostasis parameters or stimulate the immune system in patients with chronic peripheral arterial disease. In patients with VOD, treatment with defibrotide decreased plasminogen activator inhibitor 1 (PAI-1) but the change was not statistically significant when compared to

Baseline and was only observed in patients who had a complete response. No dose response effect on PAI-1 was observed.

Efficacy

Study 2005-01

The pivotal efficacy and safety study was a multicentre, non-randomised, open label, Phase III study conducted in 35 sites in the USA, Canada and Israel between 2005 and 2009, to compare clinical outcomes in 102 patients who developed severe hepatic VOD after HSCT and were treated with defibrotide, with clinical outcomes in a historical control (HC) group of patients treated with standard care, as applied at the time in the study centres. Retrospective chart reviews of 6867 patients from the enrolling study centres, who received HSCT between 1995 and 2007, applied stringent inclusion and exclusion criteria to identify a final cohort of 32 HC patients with hepatic VOD that matched the treatment group. An independent medical review committee (MRC) reviewed the identified files to confirm that the groups were appropriately matched. The majority of the HC patients were included based on transplantations that occurred between years 2000 and 2006. The ability to recruit additional HC patients was limited as defibrotide was becoming established as a treatment option under emergency use provisions, and treating physicians were not prepared to deny a clinically acceptable treatment option to seriously ill patients. The defibrotide group was dosed at 6.25 mg/kg IV infusion every six hours (q6h), with a total daily dose of 25 mg/kg, for a minimum of 21 days. Treatment was suspended for toxicity or delayed for necessary medical or surgical interventions.

Overall, the defibrotide and HC groups were well balanced with respect to the baseline demographic variables of gender, race, age, weight, body mass index (BMI), and length of hospitalisation. The baseline prognostic factors of survival at study entry included age (≤ 16 versus > 16 years), transplant type (allogeneic or autologous HSCT), and number of previous HSCTs (0 versus ≥ 1). These were also comparable between the defibrotide and final HC group. The following differences at Baseline were identified:

- a larger proportion of subjects in the defibrotide group received sirolimus or tacrolimus as prophylactic treatment for graft versus host disease (GvHD), at 49.0% (defibrotide) versus 15.6% (HC); and a larger proportion of HC group patients were treated with any other GvHD prophylaxis, 68.8% (HC) versus 39.2% (defibrotide).
- a higher percentage of patients in the defibrotide group (33.3%) were ventilator and/or dialysis dependent at study entry compared with the HC group (21.9%). The difference was more marked in the paediatric population at 31.8% (defibrotide) versus 0.0% (HC))

Analysis of the primary and secondary efficacy endpoints was based on the intention to treat (ITT) population. The primary efficacy outcome was survival at Day 100 following HSCT. The survival rate was presented using binomial estimates of Wald asymptotic confidence intervals (CIs), and propensity scores were calculated and applied according to Koch. The secondary efficacy outcomes included:

- complete response (CR) rate at Day 100 following HSCT;
- survival at Day 180 following HSCT; and
- overall survival (mortality status at date of last contact).

Complete response (CR) was defined as a bilirubin decrease to < 2 mg/dL; hepatomegaly, if it developed, had returned to Baseline; right upper quadrant (RUQ) pain, if it was present, had resolved; and multi-organ failure (signs and symptoms of renal and/or pulmonary dysfunction) having resolved. A propensity-stratified Koch weighted two sided CI was applied to assess the difference in CR rates between defibrotide and HC groups.

The observed survival at Day 100 in the defibrotide group was 38.2% and in the HC group was 25.0%. Using the propensity-stratified and weighted estimate, the difference in survival between the groups was estimated to be 23% (95.1% CI, 5.2% to 40.8%, p = 0.011) as shown in Table 3.

Table 3: Study 2005-01 Summary of survival rate at Day 100 post-haematopoietic stem-cell transplantation (intent to treat analysis set)

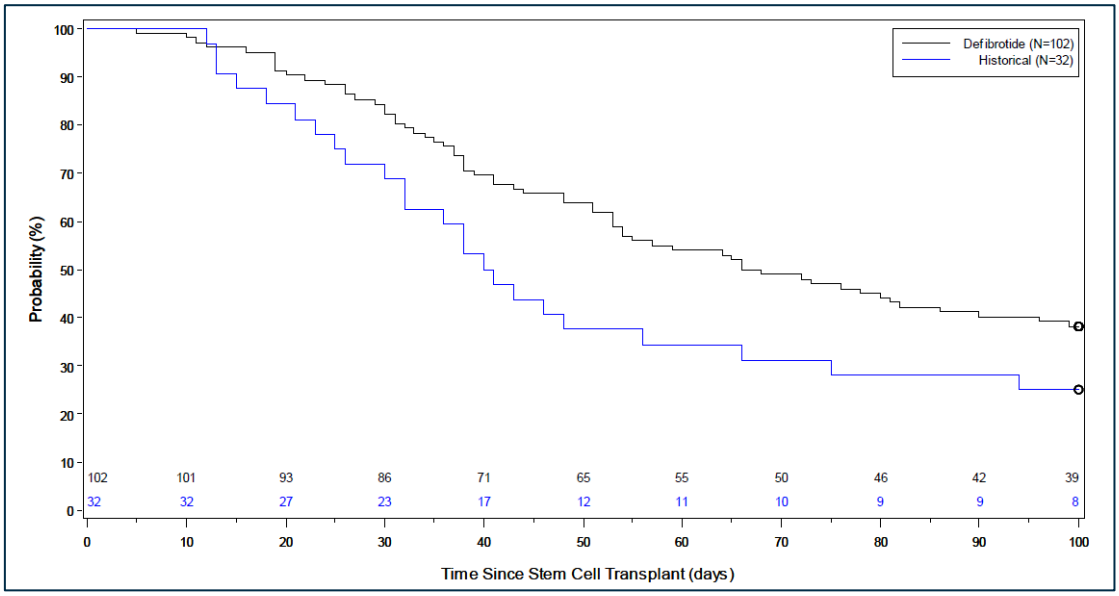
Survival rate at Day 100 post HSCT	Defibrotide group (n = 102)	Historical control group (n = 32)
Alive at Day 100 post HSCT; n (%)	39 (38.2)	8 (25)
95.1% CI; (%)	28.8 to 47.7	9.9 to 40.1
Difference in Rate (a)	23%	
95.1% CI; (%)	5.2 to 40.8	
P-value	0.0109	

(a): CI weighted by propensity score quintile for membership in the defibrotide or Historical Control group.

Note: The proportion surviving 100 days and CI are calculated using binomial estimates with Wald asymptotic CIs. For the propensity stratified and weighted estimate of difference of Day 100 survival proportions, CI and p-value are calculated using the Koch method.

Supportive efficacy analyses for Day 100 survival included both a propensity score stratified (not weighted) estimate and an unadjusted estimate of differences in survival rates using both Kaplan-Meier estimates and straight percentages (see Figure 2). The investigators concluded that defibrotide significantly improves survival at Day 100.

Figure 2: Study 2005-01 Survival at Day 100 post-haematopoietic stem-cell transplantation (intent to treat analysis set)



Defibrotide: Failed = 63 (61.8%), Censored = 39 (38.2%) and Historical Control: Failed = 24 (75.0%), Censored = 8 (25.0%)

Note: Number at risk shown in first line for defibrotide and in second line for Historical Control.

In the defibrotide group, CR rate at Day 100 was 25.5% and in the HC group was 12.5%. The Koch adjusted estimate of the differences in CR rates was 19% (95.1% CI, 3.5 to 34.6, p = 0.016) as shown in Table 4.

Table 4: Study 2005-01 Summary of complete response rate by Day 100 post-haematopoietic stem-cell transplantation (intent to treat analysis set)

Complete Response Rate by Day 100 Post-HSCT	Defibrotide group (n = 102)	Historical control group (n = 32)
Complete response by Day 100 post-HSCT; n (%)	26 (25.5)	4 (12.5)
95.1% CI; (%)	17.0 to 34.0	1.0 to 24.0
Difference in Rate (a)	19%	
95.1% CI; (%)	3.5 to 34.6	
p-value	0.0160	

(a): CI weighted by propensity score quintile for membership in the defibrotide or historical control arm.

Note: The proportion of complete response by 100 days and CIs are calculated using binomial estimates with Wald asymtptotic CIs. For the propensity stratified and weighted estimate of difference of Day + 100 complete response proportions, CI and p-value are calculated using the Koch method.

While there was a trend toward increased survival at Day 180 in the defibrotide group over the HC group, this was not statistically significant (see Table 5).

Table 5: Study 2005-01 Summary of survival at Day 180 post haematopoietic stem-cell transplantation (intent to treat analysis set)

Survival at Day 180 post-HSCT	Defibrotide group (n = 102)	Historical control group (n = 32)
Complete response by Day 180 post-HSCT; n (%)	33 (32.4)	8 (25.0)
95.1% CI; (%)	23.2 to 41.5	9.9 to 40.1
Difference in Rate (a)	16.4%	
95.1% CI; (%)	-1.2 to 34.1	
p-value	0.0669	

(a): CI weighted by propensity score quintile for membership in the Defibrotide or historical control arm.

Note: The proportion surviving 180 days and CIs are calculated using binomial estimates with Wald asymptotic CIs. For the propensity stratified and weighted estimate of difference of Day 180 survival proportions, CI and p-value are calculated using the Koch method.

The overall survival rate in the defibrotide group was 21.6% and in the HC group was 21.9%. As a statistically significant difference was not demonstrated in survival at Day 180 between the treatment and HC group, no further statistical analysis was appropriate.

Supporting studies

The other efficacy studies included in the submission were of variable quality, and provided mixed outcomes. They comprised a dose finding study (Study 99-118), an

analysis of Centre for International Blood and Marrow Transplant Research (CIBMTR) registry data, and reports from an expanded access program (Study 2006-05) and from a Defitelio - compassionate use program (DR-CUP) report. Most studies included patients with VOD as well as severe VOD and applied a variety of doses and dose regimens for defibrotide (up to 80 mg/kg/day). Not all collected complete data on all of the participants. The evaluator was able to identify a small subset of patients, who had severe VOD and received the recommended dose of 25 mg/kg/day, in two of the study reports. Two additional studies were relevant only to safety data; one study that was stopped owing to poor enrolment (Study DF-VOD) and one study of VOD prophylaxis in children (Study 2004-00592-33).

Study 99-118 was a randomised, open label, dose finding study, that evaluated the efficacy and safety of two doses of defibrotide, 25 mg/kg/day and 40 mg/kg/day, given as divided doses q6h for at least 14 days, to 149 patients with severe VOD or with VOD at high risk of developing MOD. The authors reported that 35 (46.7%) of 75 subjects in the 25 mg/kg/day treatment arm and 30 (40.5%) of 74 subjects in the 40 mg/kg/day treatment arm were considered to have achieved a CR.

The expanded access program (Study 2006-05) was an open-label study in the USA that mandated additional data reporting by physicians requesting access to defibrotide for their patients for any indication. The investigators reported that in a subset of 512 patients who developed VOD with MOF following HSCT, 247 (48.2%, 95% CI, 43.9% to 52.6%) treated with defibrotide were alive at Day 100. Day 100 status was not available for 10 (2.0%) participants. The Kaplan- Meier estimated survival rate at Day 100 post-HSCT was 49.5% (95% CI, 45.0% to 53.8%).

A report from the CIBMTR database identified that of 8341 recipients of HSCT between 1 November 2008 and 31 December 2011, 96 patients developed severe VOD with MOF. Among those, 41 had been treated with defibrotide (dose and duration not available) and 16 (39%) of those had survived to Day 100 following HSCT, whereas 31% of patients with severe VOD with MOF not treated with defibrotide survived to Day 100.

In the DF-CUP, while treating physicians were requested to complete and return clinical report forms to the sponsor, this was not mandatory. Nevertheless, clinical report forms were returned to the sponsor for 710 of 1129 patients, who had been treated with various defibrotide doses at the discretion of the physician. A Kaplan-Meier estimate of survival at Day 100 for 292 patients with severe VOD treated with 25 mg/kg/day defibrotide was 57.6%. In patients treated with the higher dose of 40 mg/kg/day, for whom data had been provided to the sponsor, the estimated survival at Day 100 was 53.9%.

In general, the additional studies appear to support claims for efficacy of defibrotide in treating severe VOD.

Paediatric data

According to the literature, paediatric patients are at greater risk of severe VOD post HSCT than adults, and this is particularly so for children under the age of 7 years.[7]

The recommended dose of defibrotide for children aged one month and up to 18 years is the same as for adults. The submission included clinical trial data for over 250 children aged between 28 days and 17 years. Paediatric patients (≤ 16 years) represented 43.1% of participants in Study 2005-01, 29.3% of participants in Study 99-118 and 53.8% of participants in Study 2006-05. Survival at Day 100 post-HSCT for paediatric patients ranged between 49.7% and 68.2% in the three studies, but estimates by sub-groups based on age: infants/toddlers (less than two years), children (2 to 11 years age) or adolescents

[7] Negrin RS, Bonis PAL Diagnosis of hepatic sinusoidal obstruction syndrome (veno-occlusive disease) following hematopoietic cell transplantation, UpToDate, last updated Mar 04, 2019.

(12 to 16 years) varied widely between the studies owing to the relatively small numbers in the studies (see Table 6).

Table 6: Survival at Day 100 by paediatric subgroups, evidence of multi-organ dysfunction (25 mg/kg/day) in patients with veno-occlusive disease post-haematopoietic stem-cell transplantation

Status, n (%)	Defibrotide 25 mg/kg/day			
	2005-01 (n = 102)	99-118 (n = 75)	2006-05 (n = 351)	Total Defibrotide (n = 528)
Adult (> 16 years)				
N (%) in respective study	58 (56.9)	53 (70.7)	162 (46.2)	273 (51.7)
Survival at Day + 100 (%)	17 (29.3)	18 (34.0)	65 (40.1)	100 (36.6)
Paediatric (≤ 16 years)				
N (%) in respective study	44 (43.1)	22 (29.3)	189 (53.8)	255 (48.3)
Survival at Day + 100 (%)	22 (50.0)	15 (68.2)	94 (49.7)	131 (51.4)
Infants/toddlers (0 to 23 months)				
N (%) in respective study	17 (38.6)	5 (22.7)	54 (28.6)	76 (29.8)
Survival at Day + 100 (%)	4 (23.5)	3 (60.0)	33 (61.1)	40 (52.6)
Children (2 to 11 years)				
N (%) in respective study	17 (38.6)	13 (59.1)	94 (49.7)	124 (48.6)
Survival at Day + 100 (%)	12 (70.6)	9 (69.2)	45 (47.9)	66 (53.2)
Adolescents (12 to 16 years)				
N (%) in respective study	10 (22.7)	4 (18.2)	41 (21.7)	55 (21.6)
Survival at Day + 100 (%)	6 (60.0)	3 (75.0)	16 (39.0)	25 (45.5)

Source: adapted from the integrated summary of efficacy, Tables 42 and 43 (sponsor submitted dossier).

The dose-finding Study 99-118 subgroup analysis showed that, although not statistically significant, paediatric patients in the 25 mg/kg/day treatment arm demonstrated a higher CR rate than those in the 40 mg/kg/day arm (68.2% versus 43.5%; p = 0.1024). Similarly, estimated survival at Day 100 was 68.2% for paediatric patients in the lower dose arm compared with 34.8% in the higher dose arm; p = 0.511. The clinical evaluator noted that the number of patients in the paediatric subgroups were small, as would be expected for an orphan drug, and commented that wide confidence intervals for the clinical outcomes make interpretation difficult; nevertheless, the results appeared consistently favourable.

Safety

The early academic PK studies did not report safety. The total patient population in the sponsor's summary of clinical safety consisted of:

- Severe VOD following HSCT population; 769 participants in Studies 2005-01; 99-118; and 2006-05, with VOD post-HSCT with evidence of MOD, who received any dose of defibrotide (n = 769). In this population, 694 participants were treated with 25 mg/kg/day defibrotide
- All VOD population; 1,405 participants in Studies 2005-01; 99-118; and 2006-05, with VOD following any treatment, with or without evidence of MOD, who received any dose of defibrotide. In this population, 1,330 participants were treated with 25 mg/kg/day defibrotide.

The data was presented in the summary in two pools:

- Pool A included data from two studies (Study 2005-01 and Study 99-118) that exclusively enrolled subjects with severe VOD following HSCT and recommended 21 days duration of treatment. The pool A population included 176 patients who had severe VOD following HSCT and received 25 mg/kg/day. Safety data for the HC group in Study 2005-01 are also included in some of the tables below.
- Pool B included data from studies that treated patients with VOD secondary to any treatment, with or without MOF.

Additional safety data was provided in the CIBMTR report, DF-CUP report, Study 2004-00592-33, Study DF-VOD and one clinical pharmacology study. Exposure to defibrotide in all clinical studies is summarised in Table 7.

Table 7: Exposure to defibrotide in all clinical studies

Study	Total daily dose	Number of subjects exposed to defibrotide			
		Severe VOD following HSCT	All VOD[a]	Other[b]	Total
2005-01	25 mg/kg	102	102	–	102
99-118	25 mg/kg[c]	74	74	–	74
	40 mg/kg[c]	75[d]	75[d]	–	75[d]
2006-05	25 mg/kg	518[e]	1137	17	1154
DF-CUP	10 mg/kg	–	85	–	85
	25 mg/kg	–	272	–	272
	40 mg/kg	–	226	–	226
	60/80 mg/kg	–	55	–	55
	Unknown	–	72	–	72

Study		Total daily dose	Number of subjects exposed to defibrotide			
			Severe VOD following HSCT	All VOD[a]	Other[b]	Total
2004-000592-3300592-33	Treatment	25 mg/kg	–	–	177	213
	Prophylaxis	25 mg/kg	–	–	60	
R09-1425		6.25/15 mg/kg	–	–	52	52
DF VOD-2012-03-PKRen		25 mg/kg	–	–	12	12
		2 × 6.25 mg/kg[g]	–	–	6	6
Total subjects			769	2098	300[f]	2398[f]
Total subjects who received defibrotide 25 mg/kg/day			694	1585	242[f]	1827[f]

a May include subjects with VOD with evidence of multi-organ dysfunction following HSCT; however, criteria were not specified or confirmatory data not available. Category includes subjects with VOD without evidence of multi-organ dysfunction and VOD not following HSCT.
b Includes studies for which defibrotide was administered as prophylaxis (Study 2004),to healthy volunteers (Studies R09-1425 and DF VOD-2012-03-PKRen), and to subjects with severe to ESRD (Study DF VOD-2012-03-PKRen).
c All subjects received a total defibrotide dose of 10 mg/kg/day IV in 4 divided doses on Day 1.
d One subject who was randomised to receive 25 mg/kg/day defibrotide was receiving approximately 40 mg/kg/day based on defibrotide serum/plasma levels. This subject is included in the 25 mg/kg/day group for the disposition, demographic, and efficacy analyses, but is included in the 40 mg/kg/day group for the safety analyses.
e Six additional subjects from Study 2006-05 are included in the integrated safety analyses for the indication population and severe VOD following HSCT population (n = 518 from Study 2006-05 for each) than are included in ITT efficacy population (all subjects in the safety population who developed severe VOD) for the individual study results (n = 512) due to differences in the algorithms to identify subjects with severe VOD following HSCT between the final Study 2006-05 analysis and the integrated analysis.
f Subjects who received defibrotide as both prophylaxis and treatment (n = 24) are counted only once in the total column.
g Two doses of defibrotide 6.25 mg/kg administered by IV infusion over 2 hours: 1 dose on a non-dialysis day (Day 1) and 1 dose on a dialysis day (Day 4).

The clinical evaluator noted that in Study 2005-01, events that were expected following transplant in the defibrotide treated group were generally not recorded as adverse events (AEs). These included stomatitis, mucositis, infection, febrile neutropenia, fatigue, loss of appetite, cytopaenias, electrolyte disturbances, hypertension, abnormal lipid profiles, pneumonitis/pulmonary infiltrates, pericardial effusion, and dyspnoea. In addition, the following symptoms of severe VOD were not recorded as AEs: hyperbilirubinemia, elevated creatinine/renal failure, weight gain, encephalopathy, hypoxia/respiratory failure, ascites, hepatomegaly, and right upper quadrant pain. However, any AE that was considered serious was recorded for the defibrotide group, and haemorrhage (any origin) and hypotension were nominated as AEs of special interest.

Pool A

Treatment emergent adverse events (TEAEs) were reported in 96% (169 out of 176) of subjects treated with 25 mg/kg/day defibrotide and in 100% of the HC group. The most frequently reported TEAEs (≥ 10% of subjects) in the defibrotide 25 mg/kg/day group

were hypotension, diarrhoea, MOF, vomiting, veno-occlusive liver disease, renal failure, nausea, epistaxis and respiratory failure. MOF, renal failure and VOD were the most frequently reported AEs in the defibrotide treated patients. Hypotension, diarrhoea, nausea and pleural effusion were the most frequently reported AEs in the HC group (see Table 8). Defibrotide related TEAEs were reported for 33% of subjects in the defibrotide 25 mg/kg/day group and 27% of subjects in the defibrotide 40 mg/kg/day group. When all haemorrhagic events were combined, the most commonly reported related AEs were haemorrhage and hypotension.

For noting, the sponsor provided the following justification to explain why VOD and MOF were included among the reported AEs even though they were nominally excluded from reporting by the protocol in Study 2005-01:

> 'In evaluating individual TEAEs throughout this summary, it should be noted that events of VOD (preferred term 'veno-occlusive liver disease'), organ failure (preferred terms of 'multi-organ failure', 'renal failure' and 'respiratory failure'), and certain manifestations of VOD (such as preferred terms 'hypoxia' and 'pleural effusion') are unique in that they represent components of the underlying condition being treated. While in some cases these conditions may have worsened during the study (and, thus, qualified as TEAEs), the nature of data collection also may have influenced such reports. Specifically, if a subject receiving defibrotide died on or within 30 days after the last dose of study drug, a serious TEAE was required to be reported; frequently that event was listed as (or at least included) VOD and/or MOF. Because serious TEAEs were not captured for the historical control subjects, this may have led to an imbalance in reporting of these individual preferred terms.'

Table 8: Study 2005-01 and Study 99-118 Treatment emergent adverse event reported in > 10% of subjects in any treatment group by Preferred Term in Pool A

Preferred Term, n (%)	Defibrotide 25 mg/kg/day	Defibrotide 40 mg/kg/day	Historical Control	Total Defibrotide
Number of subjects	176[a]	75[a]	32	251
At least 1 TEAE	169 (96.0)	73 (97.3)	32 (100.0)	242 (96.4)
Hypotension	65 (36.9)	30 (40.0)	16 (50.0)	95 (37.8)
Multi-organ failure	38 (21.6)	21 (28.0)	3 (9.4)	59 (23.5)
Renal failure	29 (16.5)	30 (40.0)	1 (3.1)	59 (23.5)
Veno-occlusive liver disease	32 (18.2)	27 (36.0)	2 (6.3)	59 (23.5)
Diarrhoea	43 (24.4)	15 (20.0)	12 (37.5)	58 (23.1)
Hypoxia	17 (9.7)	25 (33.3)	0	42 (16.7)

Preferred Term, n (%)	Defibrotide 25 mg/kg/day	Defibrotide 40 mg/kg/day	Historical Control	Total Defibrotide
Vomiting	31 (17.6)	8 (10.7)	8 (25.0)	39 (15.5)
Nausea	28 (15.9)	8 (10.7)	10 (31.3)	36 (14.3)
Epistaxis	24 (13.6)	9 (12.0)	5 (15.6)	33 (13.1)
Exfoliative rash	13 (7.4)	20 (26.7)	0	33 (13.1)
Gastrointestinal haemorrhage	15 (8.5)	18 (24.0)	3 (9.4)	33 (13.1)
Respiratory failure	20 (11.4)	8 (10.7)	4 (12.5)	28 (11.2)
Hypertension	17 (9.7)	9 (12.0)	1 (3.1)	26 (10.4)
Pleural effusion	12 (6.8)	11 (14.7)	6 (18.8)	23 (9.2)
Abdominal pain	11 (6.3)	11 (14.7)	7 (21.9)	22 (8.8)
Graft versus host disease	11 (6.3)	10 (13.3)	2 (6.3)	21 (8.4)
Pyrexia	17 (9.7)	4 (5.3)	9 (28.1)	21 (8.4)
Agitation	15 (8.5)	5 (6.7)	9 (28.1)	20 (8.0)
Thrombocytopenia	8 (4.5)	12 (16.0)	1 (3.1)	20 (8.0)
Lung infiltration	10 (5.7)	9 (12.0)	0	19 (7.6)
Haematuria	15 (8.5)	3 (4.0)	5 (15.6)	18 (7.2)
Confusional state	13 (7.4)	4 (5.3)	5 (15.6)	17 (6.8)
Oedema	10 (5.7)	7 (9.3)	7 (21.9)	17 (6.8)
Haemorrhage	6 (3.4)	11 (14.7)	0	17 (6.8)
Pulmonary alveolar haemorrhage	15 (8.5)	2 (2.7)	5 (15.6)	17 (6.8)
Febrile neutropenia	7 (4.0)	8 (10.7)	0	15 (6.0)
Dyspnoea	4 (2.3)	10 (13.3)	5 (15.6)	14 (5.6)
Anxiety	8 (4.5)	5 (6.7)	4 (12.5)	13 (5.2)
Peripheral oedema	13 (7.4)	0	4 (12.5)	13 (5.2)
Petechiae	9 (5.1)	2 (2.7)	9 (28.1)	11 (4.4)
Bradycardia	10 (5.7)	0	6 (18.8)	10 (4.0)

Preferred Term, n (%)	Defibrotide 25 mg/kg/day	Defibrotide 40 mg/kg/day	Historical Control	Total Defibrotide
Hyperglycaemia	7 (4.0)	3 (4.0)	4 (12.5)	10 (4.0)
Tachycardia	10 (5.7)	0	14 (43.8)	10 (4.0)
Blister	7 (4.0)	1 (1.3)	8 (25.0)	8 (3.2)
Constipation	8 (4.5)	0	5 (15.6)	8 (3.2)
Generalised oedema	8 (4.5)	0	8 (25.0)	8 (3.2)
Rash	8 (4.5)	0	7 (21.9)	8 (3.2)
Graft versus host disease in skin	7 (4.0)	0	5 (15.6)	7 (2.8)
Hypothermia	5 (2.8)	1 (1.3)	5 (15.6)	6 (2.4)
Insomnia	3 (1.7)	2 (2.7)	4 (12.5)	5 (2.0)
Tremor	4 (2.3)	0	4 (12.5)	4 (1.6)
Skin disorder	3 (1.7)	0	5 (15.6)	3 (1.2)
Alopecia	2 (1.1)	0	5 (15.6)	2 (0.8)
Coagulopathy	2 (1.1)	0	5 (15.6)	2 (0.8)
Lip haemorrhage	2 (1.1)	0	4 (12.5)	2 (0.8)
Metabolic acidosis	1 (0.6)	0	4 (12.5)	1 (0.4)
Rales	1 (0.6)	0	6 (18.8)	1 (0.4)
Fluid overload	0	0	5 (15.6)	0
Disorientation	0	0	4 (12.5)	0

Notes: TEAEs are defined as any AE starting after initiation of defibrotide treatment (defibrotide arm).

Preferred terms are listed in order of decreasing frequency in the total defibrotide column.

a One subject in Study 99-118 who was randomised to receive 25 mg/kg/day defibrotide was receiving approximately 40 mg/kg/day based on defibrotide serum/plasma levels. This subject is included in the 25 mg/kg/day group for the disposition, demographic, and efficacy analyses, but is included in the 40 mg/kg/day group for the safety analyses.

There were 328 out of 694 (47.3%) patients in pool A (25 mg/kg/day) who had a TEAE leading to death. The most commonly (> 2% of subjects) reported causes of death were MOF, VOD, respiratory failure, sepsis, renal failure, and pulmonary haemorrhage. The majority (63.8%) of subjects in this population had at least one serious TEAE. The most commonly (> 5% of subjects) reported SAEs were MOF, VOD, hypotension, respiratory failure, renal failure, and pulmonary haemorrhage. The incidence of MOF and VOD leading to death was at least two fold higher among defibrotide treated subjects compared with

historical controls, but respiratory failure, hepatic failure and hepatorenal syndrome leading to death were more common in the control population.

The most common (> 2%) TEAEs that led to permanent discontinuation of defibrotide were pulmonary alveolar haemorrhage, catheter site haemorrhage, MOF, pulmonary haemorrhage, and hypotension. Haemorrhage of any type was an AE of special interest, and in Pool A 57% of trial participants had at least one TEAE of haemorrhage, 29% had a severe or life threatening haemorrhage, and 9% had a haemorrhage leading to death. Haemorrhage predominantly involved the gastrointestinal tract, pulmonary system, renal system or central nervous system (Table 9).

Table 9: Treatment emergent adverse events of special interest (haemorrhage) reported in ≥ 1% of subjects in any treatment group by system organ class and preferred term in Pool A, Studies 2005-01 and 99-118

System Organ Class/ Preferred Term, n (%)	Defibrotide 25 mg/kg/day	Defibrotide 40 mg/kg/day	Historical Control	Total Defibrotide
Number of subjects	**176[a]**	**75[a]**	**32**	**251**
With at least 1 TEAE of haemorrhage	101 (57.4)	43 (57.3)	24 (75.0)	144 (57.4)
Blood and lymphatic system disorders	0	1 (1.3)	1 (3.1)	1 (0.4)
Splenic haemorrhage	0	1 (1.3)	0	1 (0.4)
Haemorrhagic anaemia	0	0	1 (3.1)	0
Endocrine disorders	**0**	**0**	**1 (3.1)**	**0**
Adrenal haemorrhage	0	0	1 (3.1)	0
Eye disorders	**14 (8.0)**	**3 (4.0)**	**5 (15.6)**	**17 (6.8)**
Conjunctival haemorrhage	11 (6.3)	2 (2.7)	3 (9.4)	13 (5.2)
Eye haemorrhage	1 (0.6)	1 (1.3)	1 (3.1)	2 (0.8)
Scleral haemorrhage	2 (1.1)	0	1 (3.1)	2 (0.8)
Gastrointestinal disorders	**32 (18.2)**	**21 (28.0)**	**16 (50.0)**	**53 (21.1)**
Gastrointestinal haemorrhage	15 (8.5)	18 (24.0)	3 (9.4)	33 (13.1)
Hematemesis	9 (5.1)	4 (5.3)	3 (9.4)	13 (5.2)

System Organ Class/ Preferred Term, n (%)	Defibrotide 25 mg/kg/day	Defibrotide 40 mg/kg/day	Historical Control	Total Defibrotide
Mouth haemorrhage	4 (2.3)	0	3 (9.4)	4 (1.6)
Upper gastrointestinal haemorrhage	1 (0.6)	2 (2.7)	1 (1.3)	3 (1.2)
Lip haemorrhage	2 (1.1)	0	4 (12.5)	2 (0.8)
Rectal haemorrhage	2 (1.1)	0	0	2 (0.8)
Hematochezia	1 (0.6)	0	3 (9.4)	1 (0.4)
Haemorrhoidal haemorrhage	0	1 (1.3)	0	1 (0.4)
Melena	1 (0.6)	0	2 (6.3)	1 (0.4)
Lower gastrointestinal haemorrhage	0	0	1 (3.1)	0
General disorders and administration site conditions	**10 (5.7)**	**3 (4.0)**	**0**	**13 (5.2)**
Catheter site haemorrhage	10 (5.7)	3 (4.0)	0	13 (5.2)
Injury, poisoning and procedural complications	**14 (8.0)**	**3 (4.0)**	**4 (12.5)**	**17 (6.8)**
Post-procedural haemorrhage	10 (5.7)	3 (4.0)	1 (3.1)	13 (5.2)
Subdural haemorrhage	2 (1.1)	0	0	2 (0.8)
Periorbital haemorrhage	1 (0.6)	0	2 (6.3)	1 (0.4)
Procedural haemorrhage	0	1 (1.3)	0	1 (0.4)
Wound haemorrhage	0	0	1 (3.1)	0
Investigations	**2 (1.1)**	**0**	**4 (12.5)**	**2 (0.8)**
Blood urine present	1 (0.6)	0	2 (6.3)	1 (0.4)

System Organ Class/ Preferred Term, n (%)	Defibrotide 25 mg/kg/day	Defibrotide 40 mg/kg/day	Historical Control	Total Defibrotide
Skin haemorrhage	2 (1.1)	0	0	2 (0.8)
Nail bed bleeding	0	1 (1.3)	0	1 (0.4)
Nervous system disorders	**13 (7.4)**	**0**	**1 (3.1)**	**13 (5.2)**
Haemorrhage intracranial	5 (2.8)	0	0	5 (2.0)
Central nervous system haemorrhage	3 (1.7)	0	0	3 (1.2)
Cerebral haemorrhage	3 (1.7)	0	1 (1.3)	3 (1.2)
Renal and urinary disorders	**19 (10.8)**	**3 (4.0)**	**5 (15.6)**	**22 (8.8)**
Haematuria	15 (8.5)	3 (4.0)	5 (15.6)	18 (7.2)
Cystitis haemorrhagic	5 (2.8)	0	1 (3.1)	5 (2.0)
Reproductive system and breast disorders	**4 (2.3)**	**3 (4.0)**	**1 (3.1)**	**7 (2.8)**
Vaginal haemorrhage	2 (1.1)	3 (4.0)	1 (3.1)	5 (2.0)
Respiratory, thoracic and mediastinal disorders	**45 (25.6)**	**13 (17.3)**	**11 (34.4)**	**58 (23.1)**
Epistaxis	24 (13.6)	9 (12.0)	5 (15.6)	33 (13.1)
Pulmonary alveolar haemorrhage	15 (8.5)	2 (2.7)	5 (15.6)	17 (6.8)
Pulmonary haemorrhage	7 (4.0)	3 (4.0)	0	10 (4.0)
Haemoptysis	1 (0.6)	1 (1.3)	1 (3.1)	2 (0.8)
Haemothorax	1 (0.6)	0	1 (3.1)	1 (0.4)
Bronchial haemorrhage	0	0	1 (3.1)	0

System Organ Class/ Preferred Term, n (%)	Defibrotide 25 mg/kg/day	Defibrotide 40 mg/kg/day	Historical Control	Total Defibrotide
Skin and subcutaneous tissue disorders	**13 (7.4)**	**3 (4.0)**	**11 (34.4)**	**16 (6.4)**
Petechiae	9 (5.1)	2 (2.7)	9 (28.1)	11 (4.4)
Ecchymosis	3 (1.7)	0	1 (3.1)	3 (1.2)
Purpura	2 (1.1)	0	1 (3.1)	2 (0.8)
Skin haemorrhage	2 (1.1)	0	0	2 (0.8)
Nail bed bleeding	0	1 (1.3)	0	1 (0.4)
Vascular disorders	**12 (6.8)**	**11 (14.7)**	**0**	**23 (9.2)**
Haemorrhage	6 (3.4)	11 (14.7)	0	17 (6.8)
Bloody discharge	3 (1.7)	0	0	3 (1.2)
Hematoma	3 (1.7)	0	0	3 (1.2)

Notes: TEAEs are defined as any AE starting after initiation of defibrotide treatment (defibrotide arm). SOC are listed alphabetically, with preferred terms listed within each SOC in order of decreasing frequency in the total defibrotide column.
a One subject in Study 99-118 who was randomised to receive 25 mg/kg/day defibrotide was receiving approximately 40 mg/kg/day based on defibrotide serum/plasma levels. This subject is included in the 25 mg/kg/day group for the disposition, demographic, and efficacy analyses, but is included in the 40 mg/kg/day group for the safety analyses.

Hypotension was the second AE of special interest. In pool A the incidence of hypotension was similar in the two defibrotide dose groups (37% for 25 mg/kg/day; 40% for 40 mg/kg/day), and was slightly higher in the historical control group (50%). Review of narrative details for subjects with hypotension revealed that, in almost all cases, hypotension was a manifestation of comorbidities, such as dehydration, haemorrhage, infection/sepsis, complications of renal failure/dialysis, or cortisol imbalance (due to adrenal insufficiency or prolonged corticosteroid use).

Pool B and other studies

Safety data in pool B essentially reflected the reports from pool A. The most common reported serious related TEAEs in pool B were pulmonary haemorrhage, gastrointestinal haemorrhage and pulmonary alveolar haemorrhage.

In the other studies, MOF, progression of VOD and sepsis were most frequently reported, and also were the SAEs most frequently leading to death.

Anaphylaxis has been reported in the literature for a previously marketed formulation of defibrotide being used to treat chronic venous insufficiency. In the all VOD population, six subjects reported hypersensitivity but of these, four were considered unrelated to defibrotide. As patients post-HSCT are given multiple medications it is difficult to ascribe a reaction to a single drug. The possibility of hypersensitivity is included in the PI.

Paediatric data

Adverse events among paediatric patients were generally similar to those seen in adult patients (Table 10). However, there was an apparent trend to more AE of pulmonary haemorrhage in younger patients than in adults.

Table 10: Studies 2005-01, 99-118, and 2006-05 Serious treatment emergent adverse event reported in ≥ 5% of patients in any paediatric subgroup in the 25 mg/kg dose group by System Organ Class in Pool B

System Organ Class/ Preferred Term, n (%)	Defibrotide		
	0-23m	2-11y	12-16y
Number of patients	**77**	**123**	**56**
At least 1 serious TEAE	**45 (58.4)**	**64 (52.0)**	**33 (58.9)**
Gastrointestinal disorders	**6 (7.8)**	**8 (6.5)**	**5 (8.9)**
Gastrointestinal haemorrhage	4 (5.2)	6 (4.9)	2 (3.6)
Hepatobiliary disorders	**9 (11.7)**	**10 (8.1)**	**10 (17.9)**
Veno-occlusive liver disease	7 (9.1)	7 (5.7)	6 (10.7)
Hepatic failure	1 (1.3)	0	3 (5.4)
Renal and urinary disorders	**4 (5.2)**	**8 (6.5)**	**5 (8.9)**
Renal failure	4 (2.6)	7 (5.7)	3 (5.4)
Respiratory, thoracic, and mediastinal disorders	**25 (32.5)**	**25 (20.3)**	**17 (30.4)**
Pulmonary haemorrhage	10 (13.0)	9 (7.3)	6 (10.7)
Respiratory failure	9 (11.7)	8 (6.5)	4 (7.1)
Pulmonary alveolar haemorrhage	5 (6.5)	2 (1.6)	1 (1.8)
Vascular disorders	**10 (13.0)**	**10 (8.1)**	**8 (14.3)**
Hypotension	7 (9.1)	4 (3.3)	8 (14.3)

Note: TEAE defined as any AE starting after initiation of defibrotide treatment (defibrotide arm).

In response to the finding in Study 2006-05 of the overall incidence of haemorrhagic events being slightly higher in adults compared to paediatrics (32.4% versus 27.4%, respectively) and the incidence of pulmonary haemorrhage events being higher in paediatric patients compared to adults (10.0% versus 4.3%, respectively), with the highest incidence observed in the youngest paediatric subgroup (infants/toddlers (< 2 years): 14.8%); children (2 to 11 years): 7.3%; adolescents (12 to 16 years): 11.2%) the sponsor conducted a multivariate analysis of the data from Study 2006-05.

This analysis was performed to identify potential confounding factors or risk factors for pulmonary haemorrhage (age, primary disease, HSCT form, conditioning regimen for current HSCT, pulmonary dysfunction at study entry, including ventilator dependency, and

the severity of VOD), and the investigators concluded that after adjusting for other confounding factors, young age itself was a significant risk factor for pulmonary haemorrhage in patients who develop VOD after HSCT or chemotherapy, with the highest risk observed in the 0 to 2 years. The underlying mechanism for this event is not clear. In response to negotiations with EMA, the sponsor has created a targeted questionnaire to obtain ongoing information regarding pulmonary haemorrhage among patients treated with defibrotide.

Study 2004-00592-33 was a study examining the efficacy of defibrotide as prophylaxis for VOD in paediatric patients following HSCT. While the study was not evaluated in detail from an efficacy perspective, it is worth noting that the most frequently reported TEAE in this study were VOD, GvHD, respiratory failure and pyrexia, and AEs leading to death included progression of VOD, respiratory failure, MOF, and sepsis in both defibrotide and control groups.

Overall the safety of defibrotide in children appears similar to adults but there may be differences in the paediatric subgroups with more AEs seen in the youngest children (0 to 23 months). The results and number of paediatric patients in the clinical studies should be highlighted in the PI along with the potential risk of pulmonary haemorrhage in this younger patient group.

Ten PSURs were included in the submission providing safety data from October 2013 to October 2018. The common spontaneous AEs reported are consistent with the safety data from the clinical trials.

Defibrotide has been supplied in Australia since November 2010 under the Special Access Scheme (SAS).[3] Since 2010 the sponsor has supplied 65,990 vials (about 788 patients) of defibrotide to Australian hospitals. The majority of the use has been by paediatric hospitals (78%) with the remainder by adult hospitals. Analysis of the most recent SAS reports (January 2017 to March 2019) indicate that the use of defibrotide in adults is almost exclusively for treatment of VOD. However, in children only 33.5% is for the treatment of VOD with 62.9% being used for prophylaxis (3.6% use is unknown).

Clinical evaluator's recommendation

The clinical evaluator has recommended approval for the intended use.

Risk management plan

The sponsor has provided EU-risk management plan (RMP) 7.0 (dated 19 December 2019; data lock point (DLP) 18 October 2019) and Australian specific Annex (ASA) version 1.0 (dated June 2020).

The RMP evaluator considers the summary of safety concerns acceptable. The sponsor has proposed routine and additional pharmacovigilance activities for all safety concerns. The pharmacovigilance plan includes a targeted follow up questionnaire regarding the occurrence of pulmonary haemorrhage which will be used internationally and in Australia.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 11.[8]

[8] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;

Table 11: Summary of safety concerns and their associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Haemorrhage (including, but not limited to, gastrointestinal haemorrhage, pulmonary haemorrhage and epistaxis)	✓‡	✓*†	✓	–
	Hypotension	✓	✓*†	✓	–
	Coagulopathy	✓	✓*†	✓	
	Immunogenicity (Allergic/Hypersensitivity reactions)	✓	✓*†	✓	–
Important potential risks	Injection site reactions/infections, septicaemia	✓	✓*†	–	–
	Thromboembolic events	✓	✓*†	–	–
	Immunogenicity (Generation of Anti-Nuclear Antibodies)	✓	✓*†	–	–
	Reproductive toxicity	✓	✓*†	✓	–
Missing information	Safety in pregnant or lactating women	✓	✓*†	✓	–
	Patients treated concomitantly with defibrotide and medications that increase the risk of haemorrhage (including the newer oral anti-coagulants direct thrombin and factor Xa inhibitors)	✓	✓*†	✓	–
	Patients with Grade B to D GVHD	✓	✓*†	–	–
	Patients with pre-existing liver or severe renal insufficiency (aetiologies other that VOD)	✓	✓*†	✓	–
	Patients with intrinsic lung disease	✓	✓*†	–	–
	Patients with ethnic background other than Caucasian	✓	✓*†	–	–

- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Patients over the age of 65 years	✓	✓*†	–	–
	Off label use	✓	✓*†	✓	–

The RMP evaluator recommends the following condition of registration:

> Defibrotide is to be included in the Black Triangle Scheme.[1] The sponsor should submit PSURs for a minimum three years from the date of approval.

Risk-benefit analysis

Delegate's considerations

The majority of patients who develop hepatic VOD following HSCT will experience only mild to moderate disease in which supportive care is likely to be sufficient. Between 10 to 30% of patients, particularly children, may develop severe disease characterised by rapidly rising serum bilirubin, rapid weight gain and the presence of multi-organ failure. In the application for orphan designation for defibrotide, the sponsor detailed several studies that report a high mortality rate in patients with severe VOD, including an analysis of 135 studies (including 24,920 HSCT patients) performed between 1997 and 2007, that estimated the mortality rate from severe VOD to be 84.3% (95% CI, 79.6% to 88.9%). By comparison, a study based on the Seattle Transplant Registry reported mortality rates at Day 100 of 9% for mild hepatic VOD and 23% for moderate hepatic VOD. Hepatic VOD is therefore correctly considered a life threatening condition. While improvements in recognising the pre-transplant risk factors and in supportive care have contributed to declining rates of hepatic VOD, in the application for orphan designation, the sponsor successfully argued that based on 2016 figures for HSCT, up to 262 patients could potentially develop VOD each year (with around 33%, or 87, progressing to severe VOD). Review of TGA SAS figures for 2013 to 2018 broadly align with this reported incidence, although in some cases these requests may be made for prophylactic use rather than treatment with defibrotide. It is noted that the eviQ;[9] guidelines prepared by the Cancer Institute New South Wales recommend defibrotide prophylaxis in high risk paediatric and adult patients being treated with HSCT, although evidence to support this indication has not been included in this submission.

While there is a history of use of defibrotide to treat severe VOD since 1995, the Delegate notes that the pivotal study only commenced in 2005 and the product received its first market authorisation in 2013. The clinical module of this submission is therefore based on dated studies. It was notable that at commencement of the pivotal Study 2005-01 a historical control group was required, rather than patients being randomised to defibrotide or placebo in a randomised controlled trial. This was ascribed to clinicians already considering defibrotide an acceptable treatment for VOD, and a placebo (standard care) arm no longer ethically acceptable to transplantation centres. A follow up study requested by the EMA (Study DF-VOD) was not completed for the same reason. Owing to these recruitment issues, the main study does have some weaknesses as identified above. The investigators applied very robust selection criteria to identify a population of

[9] eviQ A free resource of evidence-based, consensus driven cancer treatment protocols and information for use at the point of care. eviQ is developed for the Australian context and supports health professionals in the delivery of cancer treatments

somewhat contemporaneous (1995 to 2007) recipients of HSCT who, based on medical records, developed severe VOD and were not treated with defibrotide, in order to match the population prospectively enrolled to receive defibrotide according to defined criteria. While the populations were comparable on the basis of a range of demographic factors, it is notable that the defibrotide population was more likely to have received GvHD treatment with Sirolimus, which in combination with other medications may be associated with the development of VOD, and that this population may have been more severely ill at study inclusion, based on requirements for respiratory and renal support. The numerical improvement in survival at 100 days was supported by a numerical improvement in complete response rate (resolution of severe VOD) by 100 days in the defibrotide group, however further secondary objectives were not met, including overall survival which was numerically similar in defibrotide and historical control groups. While statistical associations were presented in the submission and in the clinical evaluation review, there are significant concerns with the statistical analyses presented for the pivotal efficacy study. These were also noted by both the FDA and EMA reviewers. The FDA evaluator included the following conclusions in the statistical evaluation report:

> 'The significance level cannot be determined due to many unplanned adaptations, for example. sample size reduction and planned/unplanned interim analyses.
>
> Koch's method does not allow for a sample size of 1 or smaller in any of the propensity score stratum and a size of 1 is observed in one of the stratum in the sponsor's primary analysis…, therefore the reviewer does not consider the sponsor's primary analysis adequate.
>
> Sensitivity analyses of Day + 100 survival rate varied by which propensity score strata were used. The nominal p-values from the sensitivity analyses ranged from [redacted], so the sensitivity analyses could not confirm the sponsor's primary analysis results.'

The EMA evaluation also raised concerns with the historical control group in the pivotal study, both its small size and comparability to the treatment group. An initial CHMP conclusion in May 2013 that defibrotide was not approvable was overturned following a re-examination meeting requested by the applicant. Following the re-examination, which also considered data from Study 2006-05 and CIBMTR, the CHMP opinion of July 2013 stated:

> 'CHMP is of the view that the benefit risk balance of the above mentioned medicinal product can be considered positive in the treatment indication on the following grounds:
>
> - The HC group cannot stand alone but it is accepted that even recent registry data indicate that patients who do not receive defibrotide still have a very high mortality rate;
> - The US treatment IND- study (2006-05) although uncontrolled indicate a beneficial effect on mortality of defibrotide;
> - The CIBMTR data support that defibrotide increases the VOD resolution rate and reduces the mortality rate;
> - External control data is the only possible comparison.'

Given the orphan status of the disease it is unlikely that further efficacy data will become available.

The risks specific to defibrotide are difficult to elucidate in patients already receiving a wide range of medications and treatments, and the safety assessment is limited by the lack of safety data from a randomised controlled trial (RCT). The preclinical data and likely pro-fibrinolytic action of defibrotide indicate that haemorrhage is a potential AE

associated with defibrotide. It should be noted however that the safety reports from the main and supportive studies included many adverse events, including haemorrhage, which may equally be a consequence of HSCT, or of GvHD.

The methodology used to collect AE data from the medical records of patients receiving HSCT and treatment for hepatic VOD in a clinical setting rather than under the protocol of a predefined clinical trial may not capture AE that are not as robustly recorded, as has been noted by the sponsor. Different AE could be recorded individually or included in a broader classification. Nevertheless, the studies included in this submission generally identified the same range of adverse events. Haemorrhage, particularly of the gastrointestinal tract and central nervous system is a documented complication of HSCT with clinically severe haemorrhage reported in 12% to 27% of all post-HSCT patients. The additional risk of bleeding proffered by defibrotide, and specifically in the paediatric population, would therefore be occurring in a clinical setting already actively monitoring for this complication. The analysis of haemorrhage risk in younger patients by subgroup is also complicated by small numbers in the subgroups.

The pre-clinical, clinical and RMP evaluators have reviewed the summary of safety concerns and noted the important missing information and agreed that this accurately reflects the current state of knowledge regarding defibrotide. The weaknesses in the data are described in the PI.

Proposed action

The Delegate had no reason to say, at this time, that the application for Defitelio should not be approved for registration.

The submission to register defibrotide includes a small number of predominantly open-label studies with methodological weaknesses, presented within the context of a database of clinical experience in treating an orphan condition. In the absence of adequate control data, Studies 2005-01, 2006-05, and 99-118 all show higher survival and CR rates at Day 100 for patients who have developed severe VOD, when considered within the context of the literature. The data is supported by registry data and findings from compassionate use programs that indicate poorer survival in patients who have not been treated with defibrotide. Defibrotide will be used in clinical settings by physicians with experience in managing severely unwell patients on multiple medications. Within this orphan context in the absence of other appropriate treatment, the Delegate agrees that the weight of the evidence is likely to suggest at least a short-term survival benefit for defibrotide in the treatment of severe VOD.

Pending advice from ACM and the sponsor's pre-ACM response, the Delegate considers the benefit/risk profile to be positive and recommends approval for the indication:

> *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 adolescents, children and infants of 1 month of age and above.*

Request for Advisory Committee on Medicines advice

1. Regarding the main clinical Study 2005-01, what are the views of the committee regarding a mixed comparator group from a number of centres that may not have shared similar protocols for 'standard treatment'?
2. What effect, if any, would the differences between the two groups at study entry have on the clinical outcomes?

3. What are the views of the committee regarding the results of *post hoc* changes to the statistical analysis plan?
4. What are the views of the committee regarding the utility of the safety reports by paediatric subgroups?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Advisory Committee considerations[10]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice

1. Regarding the main clinical Study 2005-01, what are the views of the committee regarding a mixed comparator group from a number of centres that may not have shared similar protocols for 'standard treatment'?

The ACM advised that standard treatment for VOD were generally supportive measures. The number of centres involved in clinical Study 2005-01 were large experienced centres who were major players in the world transplant community. It is unlikely slight differences in 'standard treatment' protocol will have a significant impact on the clinical outcome of the study. The ACM noted that early diagnosis and treatment, including defibrotide, is important in the treatment of VOD.

2. What effect, if any, would the differences between the two groups at study entry have on the clinical outcomes?

The ACM noted that although a higher incidence of VOD may be associated with use of Sirolimus as GvHD prophylaxis, no increase in deaths has been observed. The higher portion of patients who were ventilator/dialysis dependent suggests patients in the defibrotide treatment group may have been more severely ill at study entry. There is no clinical data or experience to suggest that the use of different GvHD prophylaxis will affect the clinical course of VOD once it is established.

3. What are the views of the committee regarding the results of post hoc changes to the statistical analysis plan?

The committee expressed concern with the small size and the possible selection bias in the HC group in the pivotal study. The numerical difference observed in the Day 100 survival between the defibrotide treatment group and the HCT group has not been confirmed with appropriate statistical approaches. The committee acknowledged that clinicians consider defibrotide as an acceptable treatment for VOD, and a placebo controlled trial with standard care is not feasible. As clinicians considered defibrotide as acceptable treatment for VOD, the control arm (standard treatment without defibrotide) of any placebo controlled trials will be considered unethical by transplant centres and further randomised controlled trials will be unlikely. The data from both the pivotal study and the

[10] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

additional supporting studies, although not statistically confirmed, appear to support the claims for efficacy of defibrotide in treatment of severe VOD. The committee is of the view that despite the flaws in the evidence provided, defibrotide appears to confer a survival advantage for the proposed indication.

4. What are the views of the committee regarding the utility of the safety reports by paediatric subgroups?

The ACM expressed concern regarding the trend to higher incidence of pulmonary haemorrhage in younger patients, especially infants, but noted that pulmonary haemorrhage is a known complication of HSCT in paediatric patients. The committee considered that the spectrum of diseases for which these patients are often treated with HSCT may also be associated with pulmonary haemorrhage. In the paediatric prophylaxis study (Study 2004-00592-33), the pattern of pulmonary haemorrhage was similar in both arms.

Advisory Committee recommendation

Overall, the ACM considered that this product had an overall positive benefit-risk profile for the 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 of 1 month of age and above*.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Defitelio (defibrotide) for 200 mg/2.5 mL concentrated solution for infusion, indicated for:

> *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.*

Specific conditions of registration applying to these goods

- Defitelio (defibrotide) is to be included in the Black Triangle Scheme. The PI (including the PI as package insert) and Consumer Medicine Information (CMI) for Defitelio must include the Black Triangle Symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product
- The Defitelio EU-RMP (version 7.0, dated 19 December 2019, DLP 18 October 2019), with ASA (version 1.0, dated June 2020), included with submission PM-2019-01763-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of PSURs.

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

- All batches of Defitelio (defibrotide) imported into Australia must comply with the product details and specifications approved during evaluation and detailed in the CPD.
- Up to five (5) initial batches of Defitelio (defibrotide) imported into Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index.

  Sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. Sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at https://www.tga.gov.au/publication/testingbiological-medicines
- This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency.[5]Certified Product Details

  The CPD, as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicine (http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm), in PDF format, for the products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change. CPDs should be emailed to Biochemistry.Testing@health.gov.au as a single PDF document.

Attachment 1. Product Information

The PI for Defitelio approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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