AWMSG Secretariat Assessment Report
Defibrotide (Defitelio®▼) 80 mg/ml concentrate for solution for infusion

This assessment report is based on evidence submitted by Jazz Pharmaceuticals on 7 November 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Defibrotide (Defitelio®▼) is indicated for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy. It is indicated in adults and in adolescents, children and infants over one month of age[2].
Dosing	The recommended dose of defibrotide is 6.25 mg/kg body weight every six hours (25 mg/kg/day). Defibrotide should be administered by intravenous infusion, over two hours, for a minimum of 21 days and continued until the symptoms and signs of severe VOD resolve. Refer to the Summary of Product Characteristics (SPC) for further dosing information[2].
Marketing authorisation date	18 October 2013[3].

2.0 DECISION CONTEXT

2.1 Background

Veno-occlusive disease (VOD) is a rare and life-threatening early complication of the conditioning treatment administered prior to haematopoietic stem cell transplantation (HSCT)[4,5]. It is characterised by clinical features of rapid weight gain, ascites, painful hepatomegaly and jaundice[1]. Approximately 14% of patients undergoing HSCT go on to develop VOD[6]. Mild or moderate VOD is usually reversible whereas severe VOD, which is estimated to occur in one-third of cases, is associated with multiple organ failure (MOF) and is associated with a mortality rate of > 80% 100 days post-HSCT[6].

Prior to the availability of defibrotide the management of VOD has been limited to best supportive care (BSC)[5]. Since 2010 defibrotide has been used in Wales to treat severe VOD on a compassionate use/named patient basis. The company has asserted that ten patients in Wales have been treated with defibrotide on this basis[1]. Its mechanism of action remains unclear, but in vitro data have suggested that defibrotide protects the vascular endothelium as well as restoring thrombo-fibrinolytic balance[2].

2.2 Comparator

The comparator included in the company submission was best supportive care (BSC).

2.3 Guidance and related advice

- British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation (BCSH/BSBMT Guideline). Diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation (2013)[4].
- European Group for Blood and Marrow Transplantation (EBMT) Handbook on Haematopoietic Stem Cell Transplantation (revised edition). Early complications after HSCT (2012)[7].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The applicant company provided data from a pivotal study (study 2005-01) which aimed to determine the efficacy and safety of defibrotide for the treatment of severe VOD in HSCT patients. As supporting evidence, the applicant company also included data from a dose finding study and a U.S. compassionate use study. Although supportive, the phase II dose finding study and the U.S. compassionate use study included doses and duration of therapy outside the licensed indication under consideration and so will not be discussed further[1].

3.1 Study 2005-01

This was a historically-controlled, open-label, multicentre, international, phase III trial to determine the efficacy and safety of defibrotide (25 mg/kg/day) for the treatment of severe VOD in HSCT patients[1,8]. Adults and children were eligible for study participation if they had a clinical diagnosis of VOD (according to the Baltimore criteria, defined by jaundice [bilirubin ≥ 2 mg/dl] and at least two of the following clinical findings: ascites, weight gain ≥ 5% above baseline weight and/or hepatomegaly) by day +21 post-HSCT[1,5]. Additionally, patients must have had severe VOD with MOF by day +28 post-HSCT[1,5]. MOF was defined as the presence of renal dysfunction and/or pulmonary dysfunction[1,5]. Patients in the active treatment group (n = 102) received 25 mg/kg/day of defibrotide in four divided doses for a minimum of 21 days[1,8]. The historical control group (n = 32) consisted of patients who were selected by a medical review committee as having severe VOD without any protocol exclusion criteria[1,8].

The primary endpoint was complete response of severe VOD (defined as total bilirubin less than 2 mg/dl and resolution of MOF) by day +100 post-HSCT [1,5,8]. The median duration of defibrotide treatment was 23 days. The study demonstrated a significant benefit in the active treatment group where a statistically higher proportion of patients had a complete response compared to the historical control group (23.5% versus 9.4%, p = 0.0131). Using a propensity-score adjusted analysis, the treatment difference was 17.3%. Secondary endpoints included survival by day +100 and day +180. Defibrotide significantly improved survival by day +100 when compared with the historical control group (treatment difference: -15.0%; 95.1% confidence interval [CI]: -32.3% to 2.3%; p = 0.034), although statistical improvement was not demonstrated by day +180 (treatment difference: -8.1% [95.1% CI: -25.1% to 8.8%] p = 0.084). A sensitivity analysis was performed and supported the results of the primary analysis[1,5,8].

3.2 Safety

Due to the clinical condition of patients at the time of study entry, and the toxicities commonly observed following HSCT, the incidence and severity of reported adverse events (AEs) is not unexpected[1,5]. The overall incidence of AEs was similar in the defibrotide and control groups with nearly all patients experiencing at least one AE with the majority experiencing at least one serious AE (Grade 3–5)[1,5]. As seriousness and severity of reported AEs were not assessed in the historical control group, a precise comparison of the incidence of serious AEs between the active treatment group and historical control group was not feasible[1].

The most common AEs reported were haemorrhage (including pulmonary haemorrhage, gastrointestinal haemorrhage, cerebral haemorrhage, epistaxis, or catheter site haemorrhage), hypotension and coagulopathy[1,5]. Treatment-related AEs occurred in 46/102 (45%) of patients in study 2005-01. Patients experienced a total of 89 treatment-related AEs, 34 of which were classed as Grade 3/4/5 severity. Ten deaths in the active treatment group were considered by the investigator to be possibly, probably or definitely related to defibrotide. All treatment-related deaths involved some component of haemorrhage. The Committee for Medicinal Products for Human Use (CHMP) noted a similar distribution of haemorrhagic events associated with death in the historical control group and that this suggested that these related events may have been components of the underlying clinical state[5].

At the time of licensing, the CHMP concluded that the data are hampered by the absence of sufficient concurrent safety data; however, no major safety signals that can be definitely attributed to defibrotide were observed[5].

3.3 AWTTC critique

- At the time of writing, defibrotide is the only approved medicine for the treatment of severe VOD following HSCT therapy and it's use is recommended in current treatment guidelines[4,7].
- There is a lack of robust controlled trial data for defibrotide, necessitating the use of external sources of historical control data; there is therefore uncertainty in terms of how closely the active treatment group and historical control group can be matched which is further compounded by the low number of patients included in the historical control group. CHMP acknowledged that a placebo-controlled study would not be feasible and in view of the concerns about the nature of the historical control group, considered additional U.S. registry and trial data. CHMP concluded that the weight of the evidence suggested that there was a survival benefit for defibrotide in the treatment of severe VOD and granted marketing authorisation under exceptional circumstances, with the condition that a registry is put in place to continuously collect safety and efficacy data, to be reported annually[5].
- The mechanism of action of defibrotide is unclear; however, a proposed mechanism of action is a weak profibrinolytic effect and this raises concerns about an increased risk of bleeding in a population where haemorrhage is already a frequent occurrence due to underlying clinical conditions[5].
- No UK or European centres were included in study 2005-01. It is therefore unclear whether the results would be fully translatable to the management of patients with severe VOD in the Welsh setting. The company assert that the results of the study are applicable to Wales as clinical practice and the conduct of HSCTs is similar across the countries where the trials were conducted to that in Wales[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis (CUA) comparing defibrotide plus BSC versus BSC alone in patients who have successfully undergone HSCT and develop severe VOD[1].

The analysis is based on a lifetime Markov model consisting of a one-year acute phase with a cycle length of one day, followed by a long-term phase with yearly cycles until death to capture long-term survival over a lifetime horizon. In the acute phase, patients enter the model at onset of severe VOD and may transition to complete response or death. Patients who achieve a complete response are assumed not to experience

recurrence of VOD. All patients still alive after one year then enter the long-term phase where they remain until death.

Efficacy data (transition probabilities) for the acute phase are based on data from the key clinical study, 2005-01 (see Section 3.1). Time spent in each health state is estimated from complete response and overall survival rates at the end of study follow-up (day +100 post-HSCT), which are extrapolated until the end of one year using Kaplan-Meier survival curves and an exponential function. In the absence of longer term survival data from the trial, survival in the first nine years of the long-term phase of the model is derived from a published single-centre study of outcomes in HSCT recipients in Sweden between 1992 and 2009[9], and survival from 11 years post-HSCT onwards is based on Welsh life tables adjusted by the relative survival ratio for HSCT obtained from a published Australian cohort study[10].

Defibrotide acquisition costs are calculated on a per mg basis using the mean dose (16.42 mg/kg/day), patient body weight (53.7 kg) and duration of treatment (23.3 days) observed in study 2005-01. A confidential discount on the list price of defibrotide is applied based on an agreed Wales Patient Access Scheme (WPAS). For each of the treatment arms, the difference between time to complete response by day +100 post-HSCT in study 2005-01 and the average length of stay for a HSCT in England and Wales was calculated to determine the excess number of days spent in hospital due to severe VOD. These are costed using Welsh unit costs, assuming 85% of this time would be spent in the intensive care unit (ICU) and 15% would be spent in a high dependency unit (HDU), based on company sought expert opinion[1]. All costs associated with BSC in both arms, any AE costs and the costs of end-of-life treatments are assumed to be included in the assumed bed day cost.

For the base case analysis, in the absence of quality-of-life data from the trial or specific utility values in the published literature, the utility value for patients with severe VOD is assumed, based on company sought expert opinion, to be the same as that for patients with acute liver failure and Model for End-Stage Liver Disease (MELD) score > 30 before liver transplantation (0.208)[11]. Those who achieve complete response are then assumed to have a utility value the same as the age-matched general population.

Costs and outcomes beyond one year are discounted at 3.5% per annum.

4.1.2 Results

The results of the base case analysis are presented in Table 1. Over a discounted lifetime horizon of analysis, using the WPAS agreed discount price, the use of defibrotide resulted in an incremental cost per quality-adjusted life year (QALY) gained versus BSC of [commercial in confidence data removed], based on an increase in total costs of [commercial in confidential data removed] and gain of 1.006 QALYs.

Table 1. Base case CUA results over lifetime horizon[1]

	Defibrotide + BSC	BSC
Excess hospital stay costs due to VOD	£37,667	£55,739
Medication costs	¶¶	£0
Total costs	¶¶	£55,739
Total LYs	4.55	3.41
Total QALYs	3.83	2.82
ICER (Cost/QALY gained)	**¶¶/QALY gained**	
Probability cost effective at WTP £20,000/QALY*	65.6%	
Probability cost effective at WTP £30,000/QALY*	95.7%	

* From probabilistic sensitivity analyses
¶¶ Commercial in confidence figures removed

ICER: incremental cost-effectiveness ratio; LY: life-year; QALY: quality-adjusted life year; WTP: willingness to pay per QALY gained

In one-way sensitivity analyses, the model outputs were most sensitive to the assumed daily dose and duration of defibrotide treatment, the average cost per inpatient excess bed day and the length of hospital stay due to severe VOD, and the discount rate for outcomes (Table 2). The incremental cost-effectiveness ratio (ICER) was relatively insensitive to variation in utility values for the severe VOD state in the range ±20% and the proportion of complete responders with defibrotide treatment or BSC explored in the range of their 95% CIs. In probabilistic sensitivity analysis (PSA), the probability of the addition of defibrotide to BSC resulting in an ICER below £20,000 per QALY was estimated to be 65.6% and below £30,000 per QALY was estimated to be 95.7%; however, survival rates at day +100 post-HSCT were not included among the variables randomly sampled in the PSA.

Scenario analyses explored alternative assumptions regarding selected elements of long-term survival post the VOD state and quality of life. An assumption of normal population survival based on Welsh life tables in the period +11 years post-HSCT moderately reduced the ICER to [commercial in confidence data removed] per QALY gained, and assuming an arbitrary 15% reduction of survival data from year two to year 10 increased the ICER to [commercial in confidence data removed] per QALY gained. Use of exploring a constant utility value for long-term survival is reported to have reduced the ICER to [commercial in confidence data removed] per QALY gained, while reducing utility values by an arbitrary 15% increased the ICER to [commercial in confidence data removed] per QALY gained.

Table 2. Key sensitivity and scenario analyses

Scenario description	Incremental cost per QALY	Plausibility considerations
Primary base case analysis	¶¶	Limited efficacy data due to rarity of condition: • Key trial data driving model not controlled; relative efficacy estimates subject to bias • Potentially overestimates survival benefit of defibrotide at day +100 post-HSCT, which is then extrapolated. This survival benefit not explored in PSA, so results of PSA are unreliable • Unclear whether data used in model reflects data from all patients enrolled in the trial (and the HCs); day +100 CR rates are much lower than survival rates, but model considers data from trial for patients who survived with CR • Modelling of survival over long-term based on several disparate sources. Not clear that extrapolation of survival is fully explored Assumes 85% of time with severe VOD is spent in ICU and 15% in HDU beds. Patients who have undergone HSCT assumed to have long-term quality of life the same as healthy individuals. Assumed dose of defibrotide reflects trial dosing but is on average somewhat less than recommended in SPC; also, costed based on per mg basis, which may potentially underestimate costs of defibrotide in practice
Discount rate on QALYs 0% to 6%	¶¶	Base case uses preferred rate of 3.5%. No reason to deviate from this rate
Alternative methods of extrapolating trial-based survival data: As base case but using hazard ratio from last observation data, applied for 1 year; Kaplan-Meier data for defibrotide up to 150 days, with semi-parametric function up to 150 days for placebo	¶¶ ¶¶	Model moderately sensitive to extrapolation of assumed survival data, but not clear if been fully explored
Average daily dose of defibrotide (range of 95% CI in trial = 14.8 to 18.1 mg/kg/day)	¶¶	Based on average trial doses; however, range somewhat lower than SPC recommended dose of 25 mg/kg/day, which must reflect significant levels of dose interruption/reduction. No analyses provided exploring the SPC-recommended dose, which would increase all ICER estimates
Average duration of defibrotide treatment (range of 95% CI from trial = 8.9 to 37.6 days)	¶¶	SPC recommends minimum treatment duration of 21 days. Base case uses 23.3 days so may be more appropriate
Length of additional hospital stay due to severe VOD in defibrotide arm (range of lower and upper limit to time to CR minus average length of stay for HSCT = 1.1 to 42.3 days)	¶¶	Model very sensitive to assumed length of hospitalisation due to VOD with defibrotide and BSC treatment, derived from study 2005-01. EPAR notes that comparisons with the HCs in that study are not sufficient[5]. Lower limits of the ranges explored seem implausible
Length of additional hospital stay due to severe VOD in BSC arm (range of lower and upper limit to time to CR	¶¶	

Scenario description	Incremental cost per QALY	Plausibility considerations
minus average length of stay for HSCT = 4.9 to 69.9 days)		
Average cost per additional inpatient bed day (range HDU bed day cost [£857] to ICU bed day cost [£1,932])	¶¶	ICER sensitive to assumption that 85% of VOD treated in ICU setting. If in practice more than 15% of time is spent in HDU/other settings the ICER increases.

¶¶ Commercial in confidence figures removed

CI: confidence interval; CR: complete response; EPAR: European public assessment report; HC: historical control; HSCT: haematopoietic stem cell transplant; HDU: high dependency unit; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life years; SPC: Summary of Product Characteristics; VOD: veno-occlusive disease

4.1.3 AWTTC critique

Severe VOD post HSCT is a rare condition and, consequently, there is a lack of robust controlled clinical trial data supporting the use of defibrotide. The company has made efforts to model the cost-effectiveness of defibrotide but there are several key limitations and uncertainties related to the lack of robust data. These include the assumed survival benefit with defibrotide, which could be overestimated in the base case and other analyses, and uncertainties in whether all relevant patient data from study 2005-01 have been adequately reflected in the model.

Collectively, the base case analysis appears subject to considerable uncertainty, and the results of the probabilistic sensitivity analysis, which should consider the joint uncertainty in all relevant parameter values, are unreliable. It is therefore not clear whether the analyses would reflect the cost-effectiveness of the use of defibrotide in practice.

Defibrotide has orphan drug status in the European Union and the company suggests it qualifies for consideration under the All Wales Medicines Strategy Group (AWMSG) policy for ultra-orphan medicines (see Section 6)[1,12].

Key strengths of the economic evidence include:

- The applicant company has made attempts to model the cost-effectiveness of defibrotide in the absence of robust, comparative, short- and long-term clinical evidence.
- Sensitivity analyses have been conducted to explore uncertainty in some key parameter values.

Key limitations and uncertainties in the economic evidence include:

- There is a lack of robust controlled trial data for defibrotide, necessitating the use of external sources of historical control data. Relative treatment effects are therefore subject to uncertainty and potential bias.
- Key data on complete response and survival at day +100 post-HSCT are derived from study 2005-01. CHMP accepted there was a survival benefit for defibrotide but considered the comparisons with the historical control group in study 2005-01 were inadequate alone to determine the relative treatment effects of defibrotide as an add-on to BSC[5]. These data may overestimate the survival benefit of defibrotide in the model:
    - The 2005-01 study data suggests a 13% absolute improvement in survival at day +100 post-HSCT, which is used in the model and extrapolated[1].
    - U.S. registry data, highlighted in the European Public Assessment Report (EPAR) as a source of data that could provide an estimate of the effect size that can be expected in clinical practice, suggest a smaller improvement in survival of 8%[5].

- Survival rates for defibrotide and historical controls (38% and 25%, respectively) were somewhat greater than complete response rates (23.5% and 9.4%, respectively) at day +100 in study 2005-01. It is not clear that the model reflects all data from all patients and historical controls in the trial.
- Sensitivity and scenario analyses do not adequately address these and other significant uncertainties inherent in the applicant company's model:
    - There is no consideration of the uncertainty in the assumed survival benefit of defibrotide in the acute phase.
    - Alternative assumptions for modelling long-term survival and alternative methods of extrapolation of the survival data have been considered separately, but the combined impact of the uncertainty in these is not explored.
    - The applicant company's approach to conducting PSA excludes the possibility of uncertainty in the survival benefits in the acute phase and the long term phase of the model, which is inappropriate, particularly in the context of the uncertainty that exists in the survival data and its extrapolation over time. The reported probabilities of cost effectiveness derived from the PSA are therefore unreliable.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-effectiveness of defibrotide relevant to the UK NHS.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on British Society for Bone Marrow Transplant registry, 109 patients underwent HSCT in Wales in 2012[13]. Adjusted for population growth, the applicant company estimates there were 110 HSCT recipients in 2014, and this will rise to 111 in each year 2016–19[1]. Assuming a published rate of VOD following HSCT of 13.7%, of which 33% is estimated to be severe[14], the applicant company estimates there would be five patients potentially eligible for treatment with defibrotide in each of the next five years. The applicant company reports that one to two patients per year already receive defibrotide on a named patient basis. Therefore, the applicant company estimates defibrotide may be used in one to five patients per year in each of the next five years. Taking the upper estimate, the applicant company anticipates uptake rates of 50% in year one, rising to 80% in years four and five[1].

Medicine acquisition costs are estimated based on the mean dose, duration of treatment and mean body weight of patients observed in study 2005-01, assuming no vial wastage and the WPAS-agreed discount on the list price. Savings in cost due to reduced hospital bed days with defibrotide compared with BSC are based on the same assumptions as used in the applicant company's economic model regarding the proportion of time spent in the ICU or HDU, and the shorter time to complete response. These savings are assumed to increase year on year per patient treated due to inflation at an average rate of 2.5% per annum[1].

5.1.2 Results

The company estimates the net budget impact in Wales in each of the next five years, taking account of the additional acquisition costs of defibrotide and the cost savings from reduced duration of hospital treatment, as in Table 3.

Table 3. Company estimates of net cost implications associated with use of defibrotide[1]

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	5	5	5	5	5
Uptake (%)	50%	60%	70%	80%	80%
Treated patients	3	3	4	4	4
Overall net cost	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ Commercial in confidence figures removed					

The applicant company has provided several alternative scenarios exploring the impact of assuming different numbers of patients and removal of the WPAS-agreed discount on the list price. Results are as would be predicted. Removal of the assumed annual inflation on bed day costs increased the net budget impact to [commercial in confidence data removed] in both years one and two; and to [commercial in confidence data removed] in each of the years three to five. Assuming defibrotide reduced hospital length of stay by only 10 days, the net costs in year one would have been [commercial in confidence data removed], rising to [commercial in confidence data removed] in year five (still assuming inflation on bed days costs of 2.5% per annum). Defibrotide would be cost saving if it reduced the length of stay by 19 days or more[1].

5.1.3 AWTTC critique

- The applicant company has adopted a pragmatic approach to estimate the number of patients eligible for treatment with defibrotide.
- Estimates of uptake are subject to uncertainty as in all budget impact analyses.
- The assumed net costs per patient are based on additional medicine acquisition costs and cost savings associated with reduced length of stay as assumed in the base case economic model. The medicine acquisition costs are based on doses observed in the study, which must reflect significant dose interruptions/reductions as these are somewhat lower than the SPC-recommended dose. These are costed on a per mg basis, which may underestimate actual drug costs in practice. The assumed reduction in hospital length of stay is subject to uncertainty due to comparisons with historical controls.
- Collectively, the net budget impact of defibrotide is subject to uncertainty. The number of patients receiving treatment in practice seems likely to remain low in each year.

5.2 Comparative unit costs

Defibrotide is the only medicine licensed for the treatment of severe VOD. The list price of defibrotide is £365 per 200 mg vial[1]. Assuming the SPC-recommended dose of 25 mg/kg/day (given as 6.25 mg/kg four times per day), a body weight of 60 kg and the SPC-recommended minimum duration of treatment of 21 days, the acquisition cost per patient treated would be around £57,700 to £61,300, depending on the extent of vial wastage. A confidential discount on the list price of defibrotide has been agreed via a WPAS.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, defibrotide (Defitelio®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that defibrotide (Defitelio®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted three ongoing studies that are likely to be available within 6–12 months:

- US IND TRIAL (NCT00628498): A single arm, open-label, phase III study to provide defibrotide to patients diagnosed with VOD[1,15].
- DF VOD-2012-03-PKREN: A two-phase trial composed of a dialysis study and a main study[1,5].
- Post Approval Safety Study: As part of the licence, the marketing authorisation holder was given a specific obligation to set up a disease registry that included patients with severe VOD treated or untreated with defibrotide[1,5].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 14 November 2014
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to ultra-orphan medicines

The applicant company suggests that defibrotide may be considered under the AWMSG policy relating to ultra-orphan medicines[1]. The policy applies to medicines with orphan designation in the EU that are licensed for the treatment of disease with a prevalence of less than 1 in 50,000 in the EU.

When reviewing the orphan designation for defibrotide, the Committee for Orphan Medicinal Products (COMP) noted the prevalence of hepatic VOD to be 0.07 per 10,000 population[16], which is less than the 1 in 50,000 threshold specified in the AWMSG policy[12]. Defibrotide is licensed for "the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive syndrome (SOS) in haematopoietic stem cell transplantation (HSCT) therapy", which COMP notes falls within the scope of the product's designated orphan indication, which is "hepatic veno-occlusive disease".

Should New Medicines Group (NMG)/AWMSG consider the ultra-orphan medicines policy to apply to defibrotide, the same criteria for clinical effectiveness and cost effectiveness of ultra-orphan medicines as those applied to other medicines will be considered, but recognising that the evidence base will necessarily be weaker. NMG/AWMSG would also recognise that the incremental cost effectiveness ratios of many ultra-orphan medicines will exceed the threshold cost-effectiveness range. In such cases, NMG/AWMSG will consider evidence on the following to inform their decisions (in descending order of priority)[12].

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of quality of life and survival.	Severe VOD has a high mortality rate (around 75% in historical controls used in study 2005-01, and 69% in US registry data).
Whether the medicine can reverse, rather than stabilise the condition.	Limited trial data and registry data demonstrate efficacy in achieving complete response and improved survival compared with BSC. The actual improvement in survival over BSC is subject to uncertainty.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy), and that this "definitive" therapy is currently in development.	No specific evidence. HSCT may be considered a definitive therapy for the underlying disease, but VOD is a complication of HSCT.
The innovative nature of the medicine. NMG/AWMSG will consider whether the medicine: • Represents a significant improvement on existing therapy (e.g. the medicine is able to treat a condition where there was previously no effective treatment) and; • Whether it can plausibly generate substantial health gains over existing treatments for the individual (e.g. > 1 quality-adjusted life-year [QALY]).	No other treatments are licensed for severe VOD; patients managed with a range of interventions as BSC. Limited trial data and registry data demonstrate efficacy in achieving complete response and improved survival compared with BSC. The actual improvement in survival over BSC is subject to uncertainty. The economic model generates QALY gains with defibrotide of around 1 QALY compared with BSC, but is subject to significant limitations, uncertainties and potential bias in favour of defibrotide.

Due to limitations of the economic evidence from the applicant company (see section 4.1.3), the most plausible estimate of the cost effectiveness of defibrotide is unclear.

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