The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**defibrotide (Defitelio®)** is accepted for use within NHS Scotland.

**Indication under review:** Treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy.

In a phase III open-label study, defibrotide was associated with improved complete response rate and survival in patients with severe VOD, compared with a historical control group.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of defibrotide. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**
**Indication**
Treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy.

**Dosing Information**
6.25mg/kg body weight every 6 hours (25mg/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 this level. Defibrotide should be administered for a minimum of 21 days and continued until the symptoms and signs of severe VOD resolve.

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

**Product availability date**
1 May 2014. Defibrotide was designated an orphan product in July 2004.

**Summary of evidence on comparative efficacy**
Severe hepatic veno-occlusive disease (VOD) is a rare, life-threatening early complication of conditioning therapy for haematopoietic stem cell therapy (SCT) with a high mortality rate. The mean overall incidence of hepatic VOD after SCT is approximately 14% (range 0 to 62%). Mild or moderate VOD is usually reversible, but the severe form, which is associated with multi-organ failure (MOF) and occurs much more rarely, is associated with a mortality rate of >80% by 100 days after SCT. Defibrotide has been used to treat severe VOD on a compassionate use/named patient basis for many years and is recommended in current treatment guidelines.

Its mechanism of action is unclear, but in vitro data suggest it protects the vascular endothelium and restores thrombo-fibrinolytic balance. It has now been licensed throughout the EU for the treatment of severe hepatic VOD.

The clinical evidence primarily derives from a phase III, open-label, historically-controlled, multicentre study to investigate the safety and efficacy of defibrotide in the treatment of severe hepatic (VOD) in haematopoietic stem cell transplant patients (study 2005-01). Eligible patients included both adults and children with a clinical diagnosis of VOD by day 21 post SCT, defined by jaundice (bilirubin ≥2mg/dL) and at least two of the following clinical findings: ascites, weight gain (≥5% above baseline), and/or hepatomegaly. In addition, patients must have had MOF by day 28 post SCT. MOF was defined as the presence of renal dysfunction (serum creatinine ≥3x lowest value post admission or creatinine clearance or glomerular filtration rate ≤40% of admission value or dialysis dependence) and/or pulmonary dysfunction (oxygen saturation ≤90% on room air or requirement for oxygen supplementation or ventilator dependence). The historical control (HC) group consisted of patients who were selected by an independent medical review committee as having severe VOD without any study exclusion criteria. Patients in the active treatment group received intravenous defibrotide 25mg/kg/day in four divided doses every 6 hours for a minimum of 21 days. Thereafter, treatment was continued as circumstances allowed or until the patient was discharged from hospital. Defibrotide could be interrupted or stopped if adverse events occurred, or delayed for necessary
A phase II, randomised, open-label, dose-finding study assessed the efficacy and safety of two doses of defibrotide in adults and children with severe hepatic VOD following haematopoietic SCT. Eligibility criteria were consistent with study 2005-01. Patients were randomised equally, stratified by age (≥18 years or <18 years) and whether or not the conditioning regimen included cyclophosphamide, to receive defibrotide 25mg/kg/day (group A) or defibrotide 40mg/kg/day (group B) for a minimum of 14 days or until achievement of complete response, progression of VOD, unacceptable toxicity or co-morbidities precluding further treatment. Defibrotide was administered by intravenous infusion every 6 hours. The primary outcome was complete response, defined as total serum bilirubin <2mg/dL after initiation of defibrotide with resolution of VOD-related MOF. Complete response was analysed in the evaluable population (n=141) and was achieved in 49% (35/72) of patients in group A and 43% (30/71) of patients in group B; the overall complete response rate was 46% (65/141) and the difference between the groups was not statistically significant. Overall, 42% (62/149) of patients in the treated population were alive at day +100 post SCT; 44% (33/75) in group A and 39% (29/74) in group B. There was no significant difference between the groups. The median duration of defibrotide treatment was 19 days in group A and 20 days in group B.

Richardson and colleagues (2002) published an analysis of 88 patients (adults and children) who received treatment with defibrotide for severe VOD in the USA between 1995 and 2001. All patients received defibrotide up to a maximum dose of 60mg/kg/day on an emergency use basis; 19 patients were recruited to the cohort retrospectively and 69 prospectively. The median age of the patients was 35 years (range 8 months to 62 years) and 29 patients (33%) were <18 years old. Complete response was observed in 36% (32/88) of patients and 35% (31/88) of patients survived to day +100 post SCT. Most of the responses were seen at doses of defibrotide of 20 to 40mg/kg per day. The median duration of defibrotide therapy was 15 days (range 1 to 139 days).

Corbacioglu and colleagues (2004) published a retrospective analysis of 45 paediatric patients (aged <20 years) with VOD after undergoing SCT from 12 European centres. This study recruited patients with mild/moderate VOD as well as severe VOD with MOF; overall 49% (22/45) of patients had severe VOD with MOF. The age of the patients ranged from 2 months to 20 years (median 8.2 years) and 19 patients (42%) were female. Patients received intravenous defibrotide at a dose of 10 to 110mg/kg/day (median 40mg/kg/day) in four divided doses. In patients with severe VOD, the complete response rate was 50% (11/22) with a day +100 survival rate of 36% (8/22).

The submitting company provided additional data from an independent US registry as further evidence of efficacy of defibrotide; this has not been published but is discussed in the European Public Assessment Report (EPAR). Over 8000 patients are included in the transplant registry,
which covered the time-period 2008 to 2011. 275 patients were reported to have VOD, of which 101 had severe VOD. Resolution of VOD occurred in 51% of patients treated with defibrotide plus standard of care (SOC), compared with 29% of patients who received SOC alone. Survival to day +100 post SCT was reported in 39% of patients with severe VOD who received defibrotide in addition to standard of care (SOC), compared with 31% of patients who received SOC alone.

**Summary of evidence on comparative safety**

Since patients were undergoing SCT for significant underlying disease, there was a high risk of clinically important adverse events based on the patients’ clinical condition at entry. The overall incidence of adverse events was similar in the defibrotide and control groups. Treatment related adverse events were reported in 45% (46/102) of patients in the defibrotide group of study 2005-01. The adverse event profile of defibrotide is described in the summary of product characteristics (SPC). The most common adverse reactions that have been reported during use of defibrotide for hepatic VOD are haemorrhage (including gastrointestinal haemorrhage, pulmonary haemorrhage, and epistaxis), hypotension and coagulopathy. Defibrotide is associated with an increased risk of haemorrhage and use of medicines that increase the risk of haemorrhage with 24 hours of administration (12 hours for unfractionated heparin) of defibrotide is not recommended. Reports of hypersensitivity (including anaphylaxis) have been reported from a previously marketed formulation of defibrotide.

**Summary of clinical effectiveness issues**

Severe hepatic VOD is an orphan condition with a high mortality rate for which no other specific drug treatment is available. Defibrotide has been used to treat severe VOD on a compassionate use/named patient basis for many years.

The principal clinical evidence is from a phase III, open-label, historically-controlled study (2005-01) that showed a complete response rate of 24% for patients who received defibrotide, compared with 9.4% for a HC group who did not receive defibrotide. Survival at day +100 post SCT was 38% for the defobrotide group, compared with 25% in the HC group, and at day +180 post SCT, 32% of debribrotide patients were alive, compared with 25% in the HC group.

There are two main weaknesses in study 2005-01, namely that it was not randomised and it used a historical control group, which raises uncertainty about how closely the prospective active treatment group and historical control groups could be matched. Also, a large proportion (54/86) of patients in the original historical control group were excluded from this group following an interim analysis, which could have led to bias in the final study results. Using the originally selected historical control group, 24% (24/102) of patients in the defibrotide group and 20% (17/86) of patients in the historical control group had a complete response, a treatment difference of 5.9% (99.1% CI: -9.8% to 22%) p=0.326. A historical control group was used due to the infeasibility of conducting a placebo-controlled study in this indication.

Supportive studies included a phase II, randomised, dose-finding study in which all patients received defibrotide, two uncontrolled cohort studies and a US patient registry. In these
studies the complete response rates for defibrotide-treated patients ranged from 36% to 50% and survival at day +100 post SCT ranged from 35% to 42%. The day +100 survival rate was relatively consistent among the studies.

There is a lack of robust evidence of efficacy, since no prospective, controlled studies are available; however, overall, the evidence suggests that defibrotide is effective in the treatment of severe hepatic VOD and improves survival at day +100 post SCT. In the main study, the survival benefit at +100 days post SCT was 13% and in the supporting US registry it was 8%. Clinical experts consulted by SMC considered that defibrotide is a therapeutic advancement due to no other effective therapy being available in this setting. Defibrotide has been used on a compassionate use/named patient basis for the treatment of severe VOD for many years and is recommended in current treatment guidelines. Patient numbers are expected to be very low in NHS Scotland.

**Summary of comparative health economic evidence**

The company submitted a cost-utility analysis comparing defibrotide to best supportive care (BSC) only, which included diuretics, analgesia, haemodialysis and mechanical ventilation. The time horizon was the lifetime of the patients (up to 74 years from the onset of severe sVOD). The economic evaluation was structured as a Markov model with two stages: (i) the acute phase to 1 year included the health states sVOD, complete response and dead, and (ii) the lifetime phase starting from year 1 with two health states, alive and dead.

The clinical data for the acute phase came from the main clinical study described above, including the historical control to represent the experience with BSC. Data on survival and complete response were extrapolated from the end of the study follow-up to the end of 1 year; this allowed estimates to be made of the proportion of patients in each arm in the different health states. For the phase beyond one year, the company proposed that acute myeloid leukaemia (AML) was a reasonable proxy for the longer-term survival of sVOD so data from that disease were used to extrapolate survival. Over the rest of the patient’s lifetime, a further extrapolation was attempted but the results were regarded as unrealistic by the company and hence age-specific mortality rates for the Scottish population were applied.

Quality of life data were not collected in the clinical study, nor were values for sVOD found in the literature; instead, an assumption was made that quality of life with sVOD was approximately the same as acute liver failure prior to a transplant (utility of 0.208). For patients with a complete response it was assumed that population norms for the UK population of the same age applied (utility of 0.946).

Resource use data were confined to medicines costs and length of stay in hospital. The medicines costs were based on the main clinical study and used the licensed dose of 25mg/kg per day and a mean duration of treatment of 23 days. A cost per 200mg vial of £365 was used. Hospital stay was not recorded in the main clinical study but the submission assumed patients would be in hospital until complete response. Data on time to complete response were taken from the study and found to be 46 days for defibrotide and 62 days for BSC. It was assumed 85% of stay with sVOD was in intensive care and 15% in high dependency care; the weighted average cost per day was thus £1,879 for Scotland.

In the base case analysis defibrotide cost an additional £26,953 over the lifetime of the patient.
(£92,836 versus £65,884) and yielded an additional 1.04 quality-adjusted life-years (QALYs) (3.95 versus 2.91). The estimated life-year gain was 1.11 (4.39 with defibrotide, 3.29 with BSC only). The cost per QALY was thus £26,029.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The PAS was a simple discount which lowered the list price of defibrotide. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However owing to commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

One-way, scenario and probabilistic analysis were supplied. In the one-way analysis, the most important variables were those that affected savings in bed-days and the total cost of defibrotide treatment e.g. duration of treatment. Utility values and proportion achieving complete response were less important. Mortality rates were not considered in the one-way analysis but a scenario analysis partly addressed this by using different extrapolation curves for years 1-7 based on later stage AML data.

The key sensitivity analyses where the cost per QALY changed to over £30k were:
- When the utility value for complete response was reduced to 0.69 instead of 0.95 the cost per QALY increased to £36k.
- When excess hospital stay with sVOD in historical control (BSC) arm was reduced to less than in the defibrotide arm the cost per QALY increased to £80k.
- Using alternative survival curves between years 1 and 7 based on later stages of AML changed the incremental QALYs from 1.04 to 0.95 (intermediate disease) and 0.78 (advanced disease). The cost per QALY increased to £29k based on intermediate AML survival and £37k based on advanced disease.
- Survival results from the clinical study were altered but this appears to have been constrained by the modelling involved. However, this did show the sensitivity of the results to this factor with the range of cost per QALY going from £14k to £59k.

In the probabilistic sensitivity analysis (PSA), the cost per QALY was less than £30k in 69% of scenarios. However, the PSA did not allow for any uncertainty relating to survival or the quality of the evidence and hence the QALY gain hardly differed from 1.04 implying almost complete certainty. Given the single-arm design and the extensive need for extrapolation, including the use of data for other diseases, this is implausible.

The committee discussed the evidence and felt there were two key issues; the plausibility of the saving on bed-days in intensive care and the plausibility of the QALY gain. The key concerns were as follows:

Savings on hospital bed-days may have been over-estimated and the results are very sensitive to this factor: the estimated saving per patient is £29k. The estimate of savings was based on a comparison of time to complete response in the two treatment arms using Kaplan-Meier plots from the clinical study. The issues were:
- The Kaplan-Meier plot does not include the experience of patients who had not reached the endpoint of complete response.
- The estimate assumes that patients are in intensive care or are discharged home (or die). In practice some will be in 'transplant beds' which (in cost terms) are analogous to high dependency beds and those in intensive care may 'step down' to these beds.
Overall, the committee recognised there was a case for some savings. However, it would have been helpful to see a more transparent approach that considered the experience of the different groups of patients (those who die, those who achieve complete response, and those who do neither at day 100) and also considered less expensive beds than intensive care alone.

There is uncertainty around the estimate of QALY gains (overall survival and quality of life) which has not been adequately explored. The committee was concerned that the approach used included a number of assumptions that were optimistic or open to challenge:

- It was assumed that the results for historical controls were a reasonable approximation to current Scottish clinical practice but there is likely to have been some improvement over time and the ‘real world’ data in the company’s submission suggested a smaller advantage in survival at 100 days.
- It was assumed that the experience of patients with AML was a reasonable approximation for survival between 1 and 6 years but data are available on the experience of survival after transplant and this would have been more appropriate.
- The long-term data on transplant patients do not support the company’s assumption that patients have a normal life expectancy and quality of life that is 95% of full health. Patients may suffer some lifetime problems, including secondary malignancies, and their life expectancy may be reduced. The utility value of 0.95 for complete responders was therefore considered to be too high.

To address these concerns the company provided further sensitivity analyses that reduced the time horizon and used a lower utility value for patients who achieved complete response. Reducing the time horizon to 30 years and using a utility value of 0.82 increased the cost per QALY to £38k. Reducing the time horizon in this analysis to 10 years increased the cost per QALY to £76k.

At several points in the economics section of the submission and in subsequent correspondence the company made the case that their analysis made assumptions that were conservative. It would have been helpful to have these drawn together in a single list for the committee to consider.

In conclusion, the committee recognised that the submission made some notable efforts to address a clinical evidence base that presented problems for an economic evaluation, but there are uncertainties with the case presented. SMC considered the likely range of cost-effectiveness ratios for defibrotide in this setting and the remaining uncertainties in the economic case. The committee considered the benefits of defibrotide in the context of the SMC decision modifiers and agreed that the criteria for a substantial improvement in life expectancy and an absence of other therapeutic options of proven benefit for the disease in question and provided by the NHS were satisfied. Although there were some limitations in the economic analysis, the committee agreed that the relatively high cost per QALY was acceptable given the expected benefits of the treatment and in the context of the decision modifiers and the orphan status of the medicine.

*Other data were also assessed but remain commercially confidential.*
Summary of patient and public involvement

The following information reflects the views of the specified Patient Information Group.

- A submission was received from Myeloma UK, a registered charity.
- Myeloma UK has received funding from several pharmaceutical companies in the past two years.
- Myeloma is an incurable, complex and destructive disease but benefit to patients can be achieved with early diagnosis and treatment, which can slow disease progression. Complications include severe bone pain, bone fractures, fatigue, frequent infection and kidney damage, all of which can substantially impact on quality of life.
- Currently available treatment for suitable patients is high dose therapy and stem cell transplant, which are intensive procedures involving lengthy hospitalisation.
- Veno-occlusive disease is an extremely severe and potentially life threatening side effect of these treatments. It is fatal in 85% of cases if left untreated. Symptoms include painful enlargement of the liver, jaundice, fluid retention and weight gain.
- Defibrotide may potentially provide a treatment for veno-occlusive disease and may also improve the quality of life of patients during and after myeloma treatments by reducing anxiety about the possibility of a fatal complication and ensuring that the benefits of the intensive treatments for myeloma are maximised.

Additional information: guidelines and protocols

The British Committee for Standards in Haematology and British Society for Bone Marrow Transplantation (BCSH/BSBMT) published a guideline on the diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation in 2013. Defibrotide is recommended at a dose of 25mg/kg/day for the treatment of veno-occlusive disease (VOD) (sinusoidal obstruction syndrome) in adults and children. Methylprednisolone may be considered with appropriate caution regarding the risk of infection. The guideline does not recommend the use of tissue plasminogen activator due to the risk of haemorrhage, and states that N-acetylcysteine is not routinely recommended due to lack of efficacy. The mainstay of supportive care in patients with VOD is judicious clinical care, particularly in the management of fluid balance.

The European School of Haematology (ESH) and European Group for Blood and Marrow Transplantation (EMBT) handbook 2012 recommends symptomatic treatment with salt and water restriction ± diuretics and use of albumin, plasma expanders and transfusions for maintenance of intravascular volumes and renal perfusion as first-line treatment for VOD. For severe VOD with MOF, specific treatment with defibrotide 6.25mg/kg every 6 hours for 14 days is recommended.
Additional information: comparators

Best supportive care. Methylprednisolone is included in guidelines as a treatment to consider but is not licensed for this indication.

Cost of relevant comparators

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<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per course (£)</th>
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<tbody>
<tr>
<td>defibrotide</td>
<td>6.25mg/kg every 6 hours for 21 days</td>
<td>69,000</td>
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Cost defibrotide per vial from the company submission and assuming a patient weight of 70kg.

Additional information: budget impact

The company estimated the population eligible for treatment to be 10 patients, with an estimated uptake of 70% in year 1 and 90% in year 5.

Without the PAS the gross impact on the medicines budget was estimated at £292k in year 1 and £367k in year 5. No savings were included in the budget impact estimate, therefore the net impact was the same as the gross impact.

Clinical experts consulted by SMC suggest there may be fewer cases per year than was estimated by the company and this would reduce the budget impact.

*Other data were also assessed but remain commercially confidential.*
References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.


4. *Commercial in Confidence


This assessment is based on data submitted by the applicant company up to and including 11 April 2014.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policies/Policy_Statements
Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.