MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
28 & 29 July 2020

Agenda Item No	4.1
National Programme	Blood and Infection
Clinical Reference Group	Blood and Marrow Transplantation CRG
URN	B04-P-C

Title
Use of defibrotide in severe veno-occlusive disease following stem cell transplant (all ages)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend the relative priority

Proposition
Routinely Commissioned This policy proposition updates B04/P/c Clinical Commissioning Policy: Use of defibrotide in severe veno-occlusive disease (VOD) following stem cell transplant published January 2015. This policy proposition seeks to extend the scope of the policy to increase access to treatment for a rare but serious complication linked to haematopoietic stem cell transplantation (HSCT), by ensuring that patients can access this treatment whenever they experience VOD.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposal is supported by an: Impact Assessment; Consultation Report; Equality and Health Inequalities

	Impact Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
4	Evidence Summary- not applicable (2 evidence papers submitted)
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment Report

No	*Metric*	*Summary from evidence review*
1.	Survival	Serious veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS) is associated with a high risk of death, hence survival is a very important outcome for patients because it takes account of any increased survival benefit resulting from treatment. Several included studies reported day 100 post-transplant survival rates. The largest of these (Kernan et al, 2018) was in 1000 adults and children who had received defibrotide as part of an expanded access treatment programme. The day 100 post-transplant survival rate in the entire population was 58.9%. A post hoc subgroup analysis comparing the timing of VOD/SOS onset (≤21 or >21 days) found no statistically significant difference (p-value not reported) between these two groups in the day 100 post-transplant survival rates. The day 100 post-transplant survival rate in the 264/1000 (26%) late-onset VOD/SOS patients was assessed to be 52.8% These findings have limitations. Results were not included from a comparator group of patients who did not receive defibrotide. It is therefore not possible to know for certain whether the outcomes observed were related to the concurrent use of other treatments or to chance and no final conclusions can be drawn about the relative effectiveness of defibrotide compared to other treatment strategies.

		In addition, post hoc analyses are less reliable than those stated a priori as data selection bias is possible. More reliance may be placed on a subgroup analysis if it was one of a small number of pre-specified analyses. It is unclear whether the study and analysis was sufficiently powered to detect a difference in outcome between treatment early and late onset treatment groups.
2.	Progression free survival	No evidence presented
3.	Mobility	No evidence presented
4.	Self-care	No evidence presented
5.	Usual activities	No evidence presented
6.	Pain	No evidence presented
7.	Anxiety / Depression	No evidence presented
8.	Replacement of more toxic treatment	No evidence presented
9.	Dependency on care giver / supporting independence	No evidence presented
10.	Safety	Adverse events are important to patients because if serious and/or common they may affect quality of life and their occurrence may outweigh the benefits associated with treatment. It is important to understand the rate and type of adverse events and/or side-effects related to defibrotide so that patients and clinicians can be fully informed before use. One included study reported adverse events. This was a randomised phase II dose-finding study conducted in adult and paediatric patients (Richardson et al, 2010). Included patients had a clinical diagnosis of VOD by day +35 post-HSCT or biopsy proven VOD or if they had portal vein flow reversal on ultrasound, jaundice and one other clinical criterion. Patient eligibility was also defined by severity criteria. Patients were randomised to receive lower dose defibrotide (25 mg/kg/day, n = 75) or higher dose defibrotide (40 mg/kg/day, n = 74) administered intravenously every 6 hours for ≥ 14 days or until complete response, progression of VOD or unacceptable toxicity was observed. There was a slightly higher rate of adverse events in the higher dose arm (10% v 7%) but this difference did not achieve

		statistical significance. No further description of the adverse events is provided. The study is limited because results were not included from a comparator group of patients who did not receive defibrotide. It is therefore not possible to know for certain whether the adverse events observed were related to the concurrent use of other treatments or to chance and no final conclusions can be drawn about the relative incidence or seriousness of adverse events associated with defibrotide compared to other treatment strategies.
11.	Delivery of intervention	No evidence presented

No	Metric	Summary from evidence review
1.	Complete response rate	Complete response rate is important to patients because it evaluates how well a patient has responded to the treatment of interest and denotes complete control of clinical manifestations and normalisation of laboratory parameters. Several included studies reported complete response rates. The largest of these (Kernan et al, 2018) in 1000 adults and children who had received defibrotide as part of an expanded access treatment programme is described in Box 1 of the preceding table above. Complete response rate was defined as total serum bilirubin < 34.2 µmol/L with resolution of VOD-related multi-organ failure. The complete response rate in the entire study population overall was 46% and there was no significant difference between the early and late VOD onset subgroups. The limitations of these findings are described in Box 1 of the preceding table above.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
The clinical commissioning policy proposition recommends defibrotide in severe veno-occlusive disease following stem cell transplant (SCT). This is an update to a previous policy which only allowed defibrotide if VOD occurred up to 21 days after the SCT. This policy proposition allows use for treatment of VOD occurring beyond 21 days which concurs with its licence. It is excluded from tariff.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Blood and Infection PoC on the 04/06/2020. It is noted that there is not a separate Evidence Review for this policy, as this was not captured as a separate document under the old policy production process that applied to the first version of this policy published in 2014/15. The evidence from the original policy has been utilised within the update to this policy, with the addition of two papers which provide further evidence to support the use of defibrotide for the treatment of VOD over 21 days post stem cell transplant. These are available on request.