MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
03 June 2020

Agenda Item No	2.2
National Programme	Blood and Infection
Clinical Reference Group	Blood and Marrow Transplant
URN	1902

Title
Plerixafor for stem cell mobilisation in adults and children

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
Routinely Commissioned Haematopoietic stem cell transplant (HSCT) replaces damaged blood cells with healthy ones. Haematopoietic stem cells are cells produced by bone marrow that can turn into different types of blood cells Before HSCT can take place, stem cell mobilisation must take place. In around 10-20% of cases, current mobilisation treatment fails. Plerixafor is currently commissioned for patients with specific blood cancers (multiple myeloma and lymphoma) in people of any age, and specific solid tumours in people aged 24 years or under, but not for patients with other blood cancers or people aged over 24 years with specific solid tumours. NHS England has revised the current policy to include routine commissioning of plerixafor in cases of a failed mobilisation attempt (rescue treatment) or in people with low levels of circulating stem cells (pre-emptive treatment) for the groups of patients that are not currently covered in the policy.

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; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care Board 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.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

Table 1

Evidence review 1: Plerixafor for stem cell mobilisation in people aged over 24 years with non-haematological solid tumours who are receiving autologous haematopoietic stem cell transplantation		
No	*Metric*	*Summary from evidence review*
1.	Survival	/
2.	Progression free survival	/
3.	Mobility	/
4.	Self-care	/
5.	Usual activities	/
6.	Pain	/
7.	Anxiety / Depression	/
8.	Replacement of more toxic treatment	/

9.	Dependency on care giver / supporting independence	/
10.	Safety	This outcome looks at the number of people using plerixafor who had adverse events during the study. These may or may not have been side effects been caused by the study treatment. No treatment-related adverse effects were reported in the study in the first study in 33 people with various non-haematological tumours. In the second study in 21 men with germ cell tumours, 8 men (38%) reported 17 adverse events felt to be possibly, probably or definitely related to plerixafor. None of the events were classified as serious. One man experienced chills, which were moderate in severity. All other adverse events were considered mild. They included diarrhoea (n=3), nausea (n=2), injection site reactions (n=3), bone pain (n=2), chills (n=1), neck pain (n=1), lip swelling (n=1), abnormal dreams (n=1), blurred vision (n=1) and fatigue (n=1). These are consistent with adverse effects listed in the plerixafor summary of product characteristics. Across the 2 studies, about 70% of people had rescue treatment (when insufficient cells are collected) and 30% had pre-emptive treatment (when not enough PBSC are circulating in the blood on the day of collection). Results were not reported separately for these groups. The results of the second study are for adults (73%) and children combined, and all diagnoses combined. The 2 studies included people both under and over 24 years of age. Both studies were small, uncontrolled, retrospective observational studies at high risk of bias and confounding. No statistical analyses were reported.
11.	Delivery of intervention	/

Table 2

No	Metric	Summary from evidence review
1.	Median CD34+ cell collection yields after mobilisation with plerixafor plus granulocyte-colony	CD34+ is the protein expressed on the peripheral blood stem cells (PBSC) that can be detected and measured. This outcome looks at the number of CD34+ cells that were typically collected after plerixafor was used to help dislodge the stem cells from the bone marrow and increase the amount circulating in the blood, which is known as mobilisation. The median value was used, which is the middle value from the range of results received across all the participants in the study. Successful mobilisation of cells from the bone marrow was defined as collection of at least 2 million CD34+ cells/kg

	stimulating factor (G-CSF, a growth factor)	during treatment with plerixafor plus G-CSF (with or without chemotherapy). In the study in 21 men with germ cell tumours, a median of 3.2 million CD34+ cells/kg were collected. In the second study in 33 people (79% male, 73% adults) with various non-haematological tumours (mainly germ cell tumours, Ewing sarcomas, Wiscott-Aldrich disease and neuroblastomas), a median of 4.1 million CD34+ cells/kg were collected.
2.	Number of participants collecting ≥2 x 106 CD34+ cells/kg	This outcome looks at the number of people in whom at least 2 million CD34+ cells/kg were collected after mobilisation using plerixafor and G-CSF (with or without chemotherapy), meaning they were potentially eligible for haematopoietic stem cell transplantation (HSCT). In the study in 21 men with germ cell tumours, at least 2 million CD34+ cells/kg were collected in 17 people (81%). In the study in 33 people with various non-haematological tumours, enough cells for transplant were collected in 28 people (85%). These results suggest that using plerixafor to help mobilise stem cells results in enough cells to proceed to HSCT in about 8 out of 10 adults with solid tumours (mainly men with germ cell tumours). See ‘Safety’ Outcome 10, Table 1 for limitations.
3.	Median peak peripheral blood CD34+cell count	This outcome looks at the maximum number of CD34+ cells typically circulating in the peripheral blood after stem cell mobilisation using plerixafor and G-CSF (with or without chemotherapy). The median value was used, which is the middle value from the range of results received across all the participants in the study. In the study in 33 people with various non-haematological tumours, the median peak CD34+ cell count was 32 million/litre (range 9 to 250 million/litre) after plerixafor treatment. This was a median 5.3-fold increase compared with baseline (4 million/litre). This suggests that treatment with plerixafor increases the number of CD34+ cells in the circulating peripheral blood, increasing the chance of collecting enough cells for HSCT. This result is for adults (73%, not all aged over 24 years) and children, and all diagnoses combined. 64% of people had rescue treatment and 36% had pre-emptive treatment. Results were not reported separately for these groups. The study was small, uncontrolled, and retrospective at high risk of bias and confounding. No statistical analyses were reported.

4.	Number of participants proceeding to first transplant	This outcome looks at the number of people who had HSCT after receiving plerixafor and G-CSF (with or without chemotherapy). In the study in 21 men with germ cell tumours, of the 17 people from whom at least 2 million CD34+ cells/kg were collected, 14 (82%) subsequently had HSCT (67% of the total study population [14/21]). Of the 3 people who did not have HSCT, 1 person died, and the reason is unknown for the other 2 people. 2 men who did not collect 2 million CD34+ cells/kg after using plerixafor had HSCT using additional cells pooled from previous collections. In the study in 33 people with various non-haematological tumours, of the 28 people from whom at least 2 million CD34+ cells/kg were collected, 19 (68%) had HSCT (58% of the total study population [19/33]). Seven of these people had germ cell tumours (all adults), 4 had Wiscott-Aldrich disease (all children), 3 had Ewing sarcomas (age unclear), 1 had neuroblastoma (age unclear) and 4 had other non-haematological diseases (all adults). It is not reported why 9 people from whom enough cells were collected did not have HSCT. These results suggest that using plerixafor to help mobilise stem cells results in HSCT in about two-thirds of adults with solid tumours (mainly men with germ cell tumours). Of the people who mobilised at least 2 million CD34+stem cells/kg in the studies about three-quarters subsequently had HSCT. See ‘Safety’ Outcome 10, Table 1 for limitations.
5.	Median time to neutrophil engraftment after first transplant	This outcome looks at the number of days for the number of neutrophils (a type of white blood cell) to recover and reach a set level (generally 0.5 x 109/L on 3 consecutive days) after HSCT (known as engraftment). The median value was used, which is the middle value from the range of results received across all the participants in the study. The neutrophils engrafted after about 11 days in both studies (range 9 to 18 days in the study in 21 men with germ cell tumours and 9 to 12 days in the study in 33 people with various non-haematological tumours). Specialists consider that this appears clinically satisfactory. See ‘Safety’ Outcome 10, Table 1 for limitations.
6.	Median time to platelet engraftment after first transplant	This outcome looks at the number of days for the number of platelets (a type of blood cell involved in blood clotting) to recover and reach a set level (generally 20 x 109/L without platelet transfusion on 3 consecutive days) after HSCT (known as engraftment). The median value was used, which is the

		middle value from the range of results received across all the participants in the study. The platelets engrafted after about 20 days (range 12 to 48 days) in the study in 21 men with germ cell tumours and 15 days (range 10 to 25 days) in the study in 33 people with various non-haematological tumours. Specialists consider that this appears clinically satisfactory. See 'Safety' Outcome 10, Table 1 for limitations.
7.	Number of participants proceeding to second transplant	This outcome looks at the number of people who needed a second HSCT after the first was unsuccessful and the stem cell graft failed. In the study in 21 men with germ cell tumours, 8 men (38%) received a second HSCT because the stem cell graft failed. None of the men experienced secondary graft failure. There were no reports of early or late failure of the first graft during the study in 33 people with various non-haematological tumours. See 'Safety' Outcome 10, Table 1 for limitations.
8.	Median time to neutrophil engraftment after second transplant	This outcome looks at the number of days for the number of neutrophils to recover and reach a set level (generally 0.5 x 109/L on 3 consecutive days) after the second HSCT. The median value was used, which is the middle value from the range of results received across all the participants in the study. The neutrophils engrafted in about 10.5 days (range 9 to 12 days) in the study in 21 men with germ cell tumours. Specialists consider that this appears clinically satisfactory.
9.	Median time to platelet engraftment after second transplant	This outcome looks at the number of days for the number of platelets to recover and reach a set level (generally 20 x 109/L without platelet transfusion on 3 consecutive days) after the second HSCT. The median value was used, which is the middle value from the range of results received across all the participants in the study. The platelets engrafted after about 24 days (range 12 to 44 days) in the study in 21 men with germ cell tumours. Specialists consider that this appears clinically satisfactory. See 'Median time to neutrophil engraftment after second transplant' Outcome 8, Table 2 for limitations.

Table 3

Evidence Review 2: Plerixafor for stem cell mobilisation in people with haematological tumours (apart from multiple myeloma and lymphoma) or haematological paraneoplastic complications who are receiving autologous haematopoietic stem cell transplantation		
No	*Metric*	*Summary from evidence review*
1.	Survival	/
2.	Progression free survival	/
3.	Mobility	/
4.	Self-care	/
5.	Usual activities	/
6.	Pain	/
7.	Anxiety / Depression	/
8.	Replacement of more toxic treatment	/
9.	Dependency on care giver / supporting independence	/
10.	Safety	This outcome looks at the number of adverse events attributable to plerixafor reported over the follow-up period. No one had adverse events attributed to plerixafor. This study was small, uncontrolled, retrospective, and observational and at high risk of bias and confounding. It is therefore not possible to draw any firm conclusions on the safety and efficacy of plerixafor. No statistical analyses were reported. It is likely that the summary of product characteristics for plerixafor provides the best evidence to predict the adverse effects likely to be seen in this patient group
11.	Delivery of intervention	/

Table 4

No	Metric	Summary from evidence review
1.	Median CD34+ cell collection yields after	CD34+ is the protein expressed on the PBSC that can be detected and measured. This outcome looks at the average number of CD34+ cells that were collected after

	mobilisation with plerixafor plus granulocyte-colony stimulating factor (G-CSF, a growth factor)	plerixafor was used to help dislodge the stem cells from the bone marrow and increase the amount circulating in the blood, which is known as mobilisation. Successful mobilisation of cells from the bone marrow was defined as collection of between 2.5 and 5.0 million CD34+ cells/kg during treatment with plerixafor plus G-CSF. In the 3 people with AL amyloidosis in the study who received rescue treatment with plerixafor, the median number of CD34+ cells collected was 5.7 x 106 cells/kg (range 2.9 to 5.9 x 106 cells/kg). Before treatment with plerixafor, the median number of cells collected with G-CSF alone in the 3 people with AL amyloidosis who received rescue treatment with plerixafor was 0.9 x 106 cells/kg (range 0.54 to 1.1 x 106 cells/kg). See 'Safety' Outcome 10, Table 3 for limitations.
2.	Number of participants collecting 2.5 to 5.0 x 106 CD34+ cells/kg	This outcome looks at the number of people in whom 2.5 to 5.0 million CD34+ cells/kg were collected after mobilisation using plerixafor and G-CSF, meaning they were potentially eligible for HSCT. In the 3 people with AL amyloidosis in the study who received rescue treatment with plerixafor, the target of 2.5 to 5.0 million CD34+ cells/kg were collected in all 3 people. These results suggest that using plerixafor to help mobilise stem cells results in enough cells to proceed to HSCT in 3 out of 3 adults with AL amyloidosis with cardiac involvement who have had inadequate response to G-CSF alone. See 'Safety' Outcome 10, Table 3 for limitations.
3.	Number of days of apheresis	This outcome looks at the total number of required stem cell collection days, also known leukapheresis days. In the study protocol, leukapheresis was given over 5 hours each day. In the 3 people with AL amyloidosis in the study who received rescue treatment with plerixafor, the median number of stem cell collection days was 2 (range 2 to 3 days) These results suggest that using plerixafor to help mobilise stem cells results in enough cells to proceed to HSCT within 3 days in people with AL amyloidosis with

		cardiac involvement who have had inadequate response to G-CSF alone. See ‘Safety’ Outcome 10, Table 3 for limitations.
4.	Number of participants proceeding to transplant	This outcome looks at the number of people who had HSCT after receiving plerixafor and G-CSF. In the 3 people with AL amyloidosis in the study who received rescue treatment with plerixafor, all 3 proceeded to HSCT. These results suggest that using plerixafor to help mobilise stem cells can result in HSCT in 3 out of 3 adults with AL amyloidosis with cardiac involvement who have had inadequate response to G-CSF alone. See ‘Safety’ Outcome 10, Table 3 for limitations.
5.	Number of days to neutrophil engraftment	This outcome looks at the average number of days for the number of neutrophils (a type of white blood cell) to recover and reach a set level after HSCT (known as engraftment). In the 3 people with AL amyloidosis in the study who received rescue treatment with plerixafor, the median number of days to neutrophil engraftment was 11 (range 9 to 12 days). These results suggest that using plerixafor in people with AL amyloidosis with cardiac involvement who have had inadequate response to G-CSF alone results in neutrophil engraftment within 12 days of HSCT. See ‘Safety’ Outcome 10, Table 3 for limitations.
6.	Number of days to platelet engraftment	This outcome looks at the average number of days for the number of platelets (a type of blood cell involved in blood clotting) to recover and reach a set level after HSCT (known as engraftment). In the 3 people with AL amyloidosis in the study who received rescue treatment with plerixafor, the median number of days to platelet engraftment was 13 (range 12 to 16 days). These results suggest that using plerixafor in people with AL amyloidosis with cardiac involvement who have had inadequate response to G-CSF alone results in platelet engraftment within 16 days of HSCT.

		See ‘Safety’ Outcome 10, Table 3 for limitations.
7.	Death	This outcome looks at the number of people who died over the follow-up period and the cause of death. One person who received rescue plerixafor died at day 224 from large bowel obstruction and septic shock. See ‘Safety’ Outcome 10, Table 3 for limitations.
8.	Grade III/IV toxicities	This outcome looks at the number of Grade III/IV toxicities (categorised according to the National Cancer Institute Common Terminology Criteria for Adverse. Events [CTCAE] v3.0) reported over the follow-up period. One participant had sepsis, renal toxicity and hyperglycaemia and another participant had hepatic toxicity. The authors reported that these adverse events were suspected to be due to underlying amyloidosis and complications of high-dose chemotherapy, neutropenia and immunosuppression, rather than plerixafor. See ‘Safety’ Outcome 10, Table 3 for limitations.

Considerations from review by Rare Disease Advisory Group
Not Applicable.

Pharmaceutical considerations
The clinical commissioning policy proposition recommends plerixafor for stem cell mobilisation in adults and children. This is an extension to the current policy which allows use of plerixafor in all types of stem cell transplant with the exception of leukaemias where it is not recommended. Some of these sit outside 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 6th May 2020