

## **PLERIXAFOR (MOZOBIL<sup>®</sup>) FOR MOBILISATION OF HAEMATOPOIETIC STEM CELLS IN CHILDREN WITH SOLID TUMOURS**

### **QUESTIONS TO BE ADDRESSED:**

1. Is plerixafor in stem cell mobilisation clinically effective in ensuring adequate stem cell mobilisation and a successful harvest in children with solid tumours, where peripheral stem cell support is a recognised treatment, compared with no intervention or with other standardised treatments?
2. Is plerixafor in stem cell mobilisation cost effective in children with solid tumours where peripheral stem cell support is a recognised treatment?

### **SUMMARY:**

#### **Background**

- Children with solid tumours may be successfully treated with high-dose chemotherapy followed by autologous peripheral stem cell support (also referred to as peripheral blood stem cell transplantation (PBSCT) or autologous haematopoietic stem cell transplantation (AHSCT)). Prior to the autologous transplant a 'mobilisation' procedure is required to increase the number of circulating peripheral blood stem cells (PBSC) in the blood compared to the resting state. These circulating PBSC can then be collected (harvested) using a cell separation procedure called apheresis. However, in a small proportion of children, it is not possible to obtain adequate cells (measured as number of CD34+ cells/kg body weight) using standard mobilisation with granulocyte colony stimulating factor (G-CSF) priming or chemotherapy plus G-CSF priming.
- Plerixafor, when combined with G-CSF, has been shown to increase the PBSC yield and can result in successful mobilisation of PBSC in adult patients who have previously failed to collect sufficient cells (rescue treatment). Plerixafor is not currently licensed for stem cell collection in children. Although it has been used off-licence in a number of paediatric cancer centres worldwide, the clinical and cost- effectiveness of this approach is not fully established.

#### **Clinical Effectiveness**

- We found no controlled studies on the effects of plerixafor in children undergoing PBSCT for solid tumours.
- We found twelve case series and five single case reports of plerixafor used in combination with G-CSF. Most of the case series involved very small numbers of patients (less than ten).
- Marschan *et al* reported the largest of these case series. They reviewed the results of PBSC mobilisation with plerixafor in 33 paediatric patients who had failed to achieve optimal CD34+ cell counts in peripheral blood after conventional mobilisation with G-CSF alone or with G-CSF plus chemotherapy. When plerixafor was added to G-CSF, 31 of 33 patients (93 percent) mobilised successfully and harvested more than  $2 \times 10^6$  CD34+ cells/kg; 17/33 (51 percent) yielded more than  $5 \times 10^6$  CD34+ cells/kg.
- The results in most of the other case series were similar, with rates of between 50 percent and 100 percent reported for successful mobilisation and collection of  $2 \times 10^6$  to  $5 \times 10^6$  CD34+ cells/kg body weight.
  - Most of these studies concluded that plerixafor has impressive efficacy and modest toxicity in paediatric patients.
  - However, because these studies were uncontrolled and there was a lot of heterogeneity in the patient population, they do not provide a true representation of the efficacy of plerixafor.

- Being small case series, it is also possible that there were more unsuccessful mobilisations that may not have been reported in these studies.

### **Cost Effectiveness**

- We found no studies on the cost-effectiveness of plerixafor as stimulant for PBSC mobilisation in children undergoing AHST for solid tumours.

### **Safety**

- Plerixafor is fairly well tolerated in adults. Common side effects include injection and infusion site reactions, nausea, diarrhoea, vomiting, and abdominal discomfort. It may also cause dizziness, headache and insomnia. Abnormal dreams and nightmares have also been reported.
- The safety profile in children is less well known as experience is limited. Most of the studies included in this review describe plerixafor as well tolerated, but there was an unusually high occurrence of psychiatric side effects in two of the studies.

## **1 Context**

### **1.1 Introduction**

High dose chemotherapy, followed by autologous peripheral blood stem cell transplantation (PBSCT) (also referred to as peripheral stem cell support) has become a standard therapeutic option for paediatric patients with a range of solid tumours such as neuroblastoma, medulloblastoma as well as in some subtypes of lymphoma.

Prior to PBSCT, a mobilisation procedure is required to increase the number of circulating PBSC in the blood compared to the resting state. These circulating PBSC can then be collected using a cell separating procedure called apheresis. There are two general approaches to stem cell mobilisation: cytokine mobilisation using cytokines such as filgrastim (granulocyte-colony stimulating factor (G-CSF)) alone or in combination, and chemomobilisation (CM), using chemotherapy, followed by cytokine administration.

A PBSC dose of  $2 \times 10^6$  CD34<sup>+</sup> cells/kg body weight (BW) is considered minimally effective for sustained engraftment, but a dose of  $5 \times 10^6$  CD34<sup>+</sup> cells/kg provides much better recovery of neutrophils and platelets and is therefore considered optimal. Approximately 10 to 20 percent of patients who require a stem cell transplant are prevented from proceeding to treatment because it is not possible to collect enough cells. This is because the success of mobilisation can be impaired by a number of concomitant factors. For example, children who have received numerous prior cycles of intensive chemotherapy or radiotherapy (particularly cranio-spinal) or both are at particularly high risk of being poor mobilisers. A second attempt to collect these cells can be tried, but it requires a hospital admission and the use of stronger chemotherapy.

Plerixafor has become recognised as the standard second-line stem cell mobilising agent in adults who fail conventional mobilisation using G-CSF. Although safety and efficacy, and dosage schedule have been established in adults particularly those with non-Hodgkin lymphoma and multiple myeloma, few studies have reported on the use of plerixafor in children.

Plerixafor is not currently licensed for stem cell collection in children, but it has been used off-licence in a number of paediatric cancer centres worldwide, with some of this experience now having been published.

The objective of the review is to establish the clinical and cost-effectiveness of plerixafor linked to the research questions as set out above.

### **1.2 Existing national policies and guidance**

We found no national policies or guidance on the use of plerixafor for stem cell mobilisation in children undergoing autologous stem cell transplantation for solid tumours.

### 2 Epidemiology

Childhood cancer is now reported to be the leading cause of death in children aged between 1 and 15 years worldwide. Malignant solid tumours constitute about 40 percent of all cancer diagnosis in children less than 15 years old and comprise a wide variety of entities with different incidence rates and histological and clinical characteristics.(1)

The Children's Cancer and Leukaemia Group reported that solid tumours in the UK accounted for 69 percent of cancer cases in children under 15 years old from 2000-2005.(2, 3)

Magnanti et al 2008 examined sex-specific patterns and temporal trends in the incidence of solid tumours in the North of England.(4) They reported that solid tumours in males aged 0–14 years were dominated by central nervous system (CNS) tumours (43.1%), with soft tissue sarcomas (14.3%) and sympathetic nervous system tumours (11.5%) being the next most predominant group. For females in the same age group, CNS tumours (39.1%), sympathetic nervous system tumours (12.0%) and renal tumours (10.7%) were the three most common types of solid tumour.(4)

In the UK lymphomas account for about 11 percent of all cancers diagnosed in children and more than twice as many cases are diagnosed in boys as in girls. Hodgkin lymphoma accounts for around 45 percent of all lymphomas diagnosed in children. Incidence increases steadily after the age of two until the last few years of childhood, where there is a much sharper increase such that more than two-thirds (71%) of all childhood Hodgkin lymphomas are diagnosed in 10–14 year-olds. Non-Hodgkin lymphoma (NHL) including Burkitt lymphoma accounts for more than half (53%) of all lymphomas in children. Incidence of NHL increases sharply in the first few years of childhood and subsequently increases more gradually with age.(5)

At least 15,000 more children have survived their cancer for at least ten years than would have done if survival had remained as it was in the early 1970s.(6) Cancer statistics in the US show that although survival rates for most childhood cancers have improved in recent decades, these rates remain very low for some cancer types, for some age groups, and for some cancers within a site. For example, among children with Wilms tumour (a type of kidney cancer), older children (those diagnosed between ages 10 and 16 years) have worse five-year survival rates than younger children. (7) For soft tissue sarcomas, five-year survival rates among children and adolescents aged 0 to 19 years range from 64 percent (rhabdomyosarcoma) to 72 percent (Ewing sarcoma), and five-year survival rates for CNS tumours range from 70 percent (medulloblastoma) to 85 percent (astrocytoma).(8)

Mortality rates for childhood cancer (including all benign, uncertain and unknown behavior brain, other CNS and intracranial tumours) have decreased overall in the UK since the mid-1970s. In males aged 0-14, worldwide age standardised (AS) mortality rates decreased by 64 percent between 1975-1977 and 2009-2011. The decline is slightly less for females aged 0-14, with rates decreasing by 54 percent between 1975-1977 and 2009-2011. This downward trend is true for all cancer types, but to varying amounts. Over the last decade (between 2000-2002 and 2009-2011), the worldwide AS mortality rates have decreased by 27 percent in males aged 0-14, but remained stable in females aged 0-14.(9)

### 3 The intervention

Plerixafor (Mozobil®, AMD3100) is a selective and reversible antagonist of the CXCR4 chemokine receptor and interferes with the interaction of CXCR4 with stromal cell-derived factor-1 (SDF-1). Formation of this complex is essential for the binding of stem cells within the bone marrow and its inhibition thus releases these cells into the peripheral blood. Unlike G-CSF, plerixafor is not a growth factor but works alongside G-CSF to release cells more efficiently. This drug was introduced into the UK in August 2009.

There are two main settings where plerixafor can be used: after a failed prior mobilisation (rescue mobilisation), and for mobilisation in patients with ongoing low CD34+ cell counts to prevent a mobilisation

and collection failure (pre-emptive use). Rescue mobilisation involves adding plerixafor to remobilisation regimens for patients who have failed at least one prior mobilisation attempt which did not involve plerixafor. In pre-emptive use, plerixafor is added to steady-state G-CSF in patients known to mobilise poorly, based on pre-apheresis CD34+ cell counts ( $<10 \times 10^6$  CD34+ cells/ml), or in patients known to collect poorly, based on earlier daily apheresis yields ( $<2 \times 10^6$  CD34+ cell/kg). The minimum target harvest per apheresis session depends on the treatment centre and on the target number of apheresis sessions per patient. In general, a yield of at least  $2 \times 10^6$  CD34+ cell/kg body weight is considered the minimum, and at least  $5 \times 10^6$  CD34+ cell/kg is considered optimum for ensuring a successful PBSCT.

Plerixafor (Mozobil®) is licensed for use in combination with granulocyte-colony stimulating factor (G-CSF) to enhance mobilisation of haematopoietic stem cells to the peripheral blood in adult patients with lymphoma and multiple myeloma whose cells mobilise poorly. It is not licensed in the UK for use in children, and paediatric data on the use of plerixafor remains considerably more limited.

## 4 Findings

We carried out a search on the evidence for the clinical and cost-effectiveness of plerixafor in children with solid tumours where PBSCT is a recognised treatment.

The search strategy employed is outlined in Section 7.

### 4.1 Evidence of effectiveness

We found no systematic reviews or controlled studies on the clinical effectiveness of plerixafor used in combination with G-CSF in children undergoing PBSCT for solid tumours.

We found twelve retrospective case series.(10-21) Most of these were single centre studies and most involved very small numbers of patients (range three to 33). We also found five single case reports which have not been included in this review and a few studies of patients across all age groups where results were not reported separately for the paediatric cases. The detail of the included studies are summarised in table 1.

- **Maschan *et al***, in the largest of the retrospective case series that we found, reviewed the results of PBSC mobilisation with plerixafor in 33 paediatric patients who failed to achieve optimal CD34+ cell counts in peripheral blood after conventional mobilisation with G-CSF alone or G-CSF plus chemotherapy (15).

These patients, who had insufficient CD34+ cell mobilisation (less than  $20 \times 10^6$  CD34+ cells/L) after four days of G-CSF (or G-CSF plus chemotherapy), were additionally stimulated with plerixafor 0.24 mg/kg subcutaneously (SC) 11-12 hours before scheduled apheresis. If sufficient dose of CD34+ cells was not collected after first apheresis procedure, plerixafor stimulation was repeated with the same dose and G-CSF was continued until the last day of apheresis.

In total 31 of 33 patients (93 percent) mobilised successfully and the median number of harvested CD34+ cells was  $5.6 \times 10^6$  CD34+ cells/kg (range  $2.7-2.74 \times 10^6$ ). 17 of 33 patients (51 percent) collected more than  $5 \times 10^6$  CD34+ cells/kg. At least 24 of 31 eligible patients underwent PBSCT; engraftment was achieved in all but one patient who died due to infection nine days after transplantation.

- The results from Maschan's study are similar to those reported in most of the other case series with rates of between 60 percent and 100 percent reported for successful mobilisation and harvests. Like Maschan, most of these authors concluded that plerixafor has impressive efficacy and modest toxicity in paediatric patients. It is however important to note that these studies were uncontrolled so the absolute effect compared with current alternatives (for example remobilising with G-CSF with/without

chemotherapy) is not known. There was also a lot of heterogeneity in the patient population as they varied in nature and degree of primary disease, degree of pre-treatment with chemotherapy and/or radiotherapy. Another limitation of small case series is that they do not provide a true representation of efficacy, in that unsuccessful mobilisations may not be reported.

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## 6 | EVIDENCE SUMMARY REPORT

**Table 1: Summary of studies**

Study	No of patients	Baseline Characteristics	Intervention	Outcome	Comment
Maschan AA <i>et al</i> (15)  Single centre retrospective case series review of all paediatric patients who received plerixafor for PBSC remobilisation (Jan 2010 to March 2014)	33	Relapsed/refractory lymphoma: n=13; Neuroblastoma: n=12; Osteosarcoma: n=3; Acute myeloid leukaemia: n=2; Germ cell tumour: n=1;  Median age: 9 yrs (range 1-18 yrs)  All patients had failed previous stem cell mobilisation with G-CSF or CM+G-CSF	G-CSF 10-20 mcg/kg (SC) for 4 days  Plerixafor 0.24 mg/kg (n=30), or 0.3 mcg/kg (n=3) 11-12 hours before apheresis  Further plerixafor dose after initial suboptimal harvested CD34 <sup>+</sup> cells (n=4)	31/33 (93%) of patients reached the minimum CD34 <sup>+</sup> cell harvest goal (>2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg); median 5.6 x 10 <sup>6</sup> CD34 <sup>+</sup> cells/kg (range 2.7-2.74).  17/33 (51%) patients reached the harvest goal (>5x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg)  At least 24/31 underwent ASCT; engraftment was achieved in all but one patient who died due to infection 9 days after HSCT.  Mild toxicity was observed in 8 (24%) patients; diarrhoea (5), nausea (1), ossalgia (1), urticaria (1)	
Son M <i>et al</i> (20)  Prospective review of high risk neuroblastoma patients scheduled for PBSC collection between January 2012 and July 2012	6	Neuroblastoma (high risk): n=9;  All patients received prior induction chemotherapy: followed by G-CSF + 2 further chemotherapy cycles following which apheresis failed to achieve a minimum target of 10 x 10 <sup>6</sup> CD34 <sup>+</sup> cells/kg over three days	G-CSF 5 mcg/kg/day until collection complete;  Plerixafor 0.24 mg/kg/day (SC) from 12 hours to first collection until day before last collection	3/6 (50%) patients achieved above the minimum harvest of 10 x 10 <sup>6</sup> CD34 <sup>+</sup> cells/kg. A median of 7.6 x 10 <sup>6</sup> cells (range 0.3-35.3) were collected over a median of 3 days of apheresis  4 patients experienced nightmares, nyctophobia and visual hallucination which, in one patient, persisted for a month.	The study title described the subjects as 'children'; the median age and age range were not provided.
Patel B <i>et al</i> (17)  Single centre retrospective case series review	5	Neuroblastoma: n=3; Medulloblastoma: n=1; Ewings Sarcoma: n=1  Median Age 4yrs (range 18 mnth – 7 yrs)  All patients were heavily pre-treated with Chemotherapy  2 patients received prior radiotherapy	G-CSF plus Plerixafor priming as primary method of stem cell mobilisation;	3/5 (60%) of patients achieved at least 6 x 10 <sup>6</sup> CD34 <sup>+</sup> positive haematopoietic stem cells following a single day of harvesting.  5/5 (100%) patients achieved at least 5 x 10 <sup>6</sup> CD34 <sup>+</sup> positive haematopoietic stem cells following a single day of harvesting.  All patients tolerated plerixafor extremely well with no obvious adverse events that could be related to plerixafor	Exact doses and regimes of priming agents are not reported.

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## 7 | EVIDENCE SUMMARY REPORT

Study	No of patients	Baseline Characteristics	Intervention	Outcome	Comment
<p>Emir S <i>et al</i> (12)</p> <p>Case series review on patients who had previously failed stem cell mobilization by chemotherapy and G-CSF for autologous transplantation between 2010 and 2012</p>	3	<p>Hodgkin's Lymphoma: n=2 Ewing's Sarcoma: n=1</p> <p>Media age: 9 yrs (range 9-14yrs)</p> <p>All three patients received multiple chemotherapy courses and one received radiotherapy</p> <p>All patients had failed previous stem cell mobilisation with G-CSF or CM + G-CSF</p>	<p>G-CSF 10-20mcg/kg (SC) for 5-14 days, continued daily until apheresis completed</p> <p>Plerixafor 240 mcg/kg for 1 – 3 doses</p>	<p>3/3 mobilized CD 34<sup>+</sup> cells (median 11.8 x 10<sup>6</sup>/kg, (range 6.34–28.47 x 10<sup>6</sup>/kg) within 2–3 cycles.</p> <p>Plerixafor was well tolerated</p>	
<p>Sevilla J <i>et al</i> (19)</p> <p>Multicentre retrospective review of patients of patients who received compassionate-use plerixafor in Spain and Italy</p>	8	<p>Ewing Sarcoma: n=2 Medulloblastoma: n=3 Hodgkin's disease: n=1 B-cell lymphoma: n=1 Systemic Lupus Erythematosus: n=1</p> <p>Median Age: 12.5 yrs (6-18yrs)</p> <p>All patients had prior multiple chemotherapy cycles; 3/8 patients had prior radiotherapy</p> <p>All patients failed prior mobilisation attempts with either G-CSF alone or G-CSF+ Chemotherapy</p>	<p>G-CSF 6.3 – 12 mcg/kg for 4-11 days (SC);</p> <p>Plerixafor 0.23 – 0.24 mg/kg for 1-4 days</p>	<p>6/8 (75%) patients reached the recommended minimum number (2 x 10<sup>6</sup> CD34<sup>+</sup> cells/kg) of progenitor cells for autologous transplantation.</p> <p>2/8 (25%) patients experienced adverse events after plerixafor use. Bone pain (n=1); anxiety, nightmares and night fever (n=1)</p>	



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## 8 | EVIDENCE SUMMARY REPORT

Study	No of patients	Baseline Characteristics	Intervention	Outcome	Comment
Pham HP <i>et al</i> (18)  Retrospective observational review of all paediatric patients who were mobilised by plerixafor in combination with G-CSF/GM-CSF between 1 December 2006 and 31 December 201	5	Neuroblastoma: n=1; Medulloblastoma: n=1; Primitive neuroectodermal tumour: n=1; Burkitt's lymphoma: n=2  Median Age 14yrs (10-20yrs)  All patients were heavily pre-treated with chemotherapy;  Two patients had prior radiation therapy; 4 had failed at least one prior mobilisation (including 1 patient with plerixafor/G-CSF)	G-CSF 10 mcg/kg (SC) for 5 days, continued daily until apheresis completed: n=4;  G-CSF 4.75 mcg/kg, GM-CSF 250 mcg/m <sup>2</sup> (SC) for 5 days, continued until apheresis completed: n=1  Plerixafor 220 – 330 mcg/kg; continued until apheresis completed (max 4 doses): n=5	4 / 5 (80%) patients achieved minimum harvest goal (2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg)  3/5 (60%) patients reached harvest goal (5x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg)	
Modak S <i>et al</i> (16)  Single centre retrospective case series	7	Stage 4 Neuroblastoma: n=7  Median Age 6 yrs (2-25yr)  All patients had at least one prior chemotherapy regimen (range 1-5); 6/7 had prior external beam radiotherapy; 2/7 had prior ASCT; 7/7 had prior priming with G-CSF (2); GM-CSF+G-CSF ((3); CM+G-CSF (2)  7/7 had inadequate Prior PBSC collection (0-1.8X10 <sup>6</sup> CD34 <sup>+</sup> cells/kg.	G-CSF 15 mcg/kg (SC) for 4 days prior to and on days of planned harvest;  Plerixafor 240 mcg/kg (SC) 11-14 hr prior to first apheresis then on each subsequent day of harvest.  Both G-CSF and plerixafor continued until harvest completed or unsuccessful	5/7 (71%) patients had successful PBSC harvest; median 7.4 (range 3.4-9.2)x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg  No acute adverse events were encountered with plerixafor administration	
Hong TK <i>et al</i> (13)  Single centre retrospective case series analysis	6	Medulloblastoma: n=2 Osteosarcoma: n=2 Ewing Sarcoma: n=1  Median Age 10.5yrs (6-15) yrs  All patients had previously failed PBSC mobilisation by chemotherapy and G-CSF.  All patients were heavily pre-treated with chemotherapy  2/6 patients had prior radiotherapy	G-CSF 10 mcg/kg (SC) for 4 days, without prior chemotherapy, then;  Plerixafor 240 mcg/kg (SC) plus G-CSF 10 mcg/kg (SC) at 10 and 2 hrs before each apheresis.	6/6 (100%) patients had successful mobilisation of stem cells. Median 11.08 CD34 <sup>+</sup> cells) x 10 <sup>6</sup> /kg (range 6.34-28.97).  7 ASCT were completed with acceptable engraftment results  3 patients were disease free at last follow up (up to 28 months)  1 patient died on day 3, while 2 MBL patients developed serious lung problems and died of respiratory failure.	



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## 9 | EVIDENCE SUMMARY REPORT

Study	No of patients	Baseline Characteristics	Intervention	Outcome	Comment
Avramova BE <i>et al</i> (11)  Single centre retrospective case series analysis	3	Metastatic germ cell tumour: n=1 Hodgkin's Disease; n=2  Age 7-18 yrs  All patients failed at least one earlier mobilisation with CM+G-CSF	G-CSF 10 mcg/kg (SC) for 4 days, then;  Plerixafor 240 mcg/kg (SC) 11 and 1 hour before apheresis	3/3 (100%) patients had successful CD34 <sup>+</sup> harvest: median 4.76 (4.76-11.3) x 10 <sup>6</sup> cells/kg after one or two apheresis.  All patients had successful myeloablative Chemotherapy followed by ASCT with full neutrophil and platelet recovery with 13 days  No patient experienced adverse events attributed to plerixafor.	
Aabideen K <i>et al</i> (10)  Single centre retrospective case series analysis	4	Neuroblastoma: n=1; Medulloblastoma: n=1; Non-Hodgkin's Lymphoma: n=1; Wilm's Tumour: n=1  Median Age : 5.5 (3-14) yrs  All patients were heavily pre-treated with chemotherapy; 2/4 patients had prior radiotherapy  All patients failed prior mobilisation with CM+G-CSF (n=1) or G-CSF (n=3)	G-CSF 10 mcg/kg (SC) x 5, then;  Plerixafor 240 mcg/kg (SC) repeated for up to 3 doses	3/5 (60%) apheresis occasions produced successful CD34 <sup>+</sup> harvest: 3.2 - 20.54 x 10 <sup>6</sup> cells/kg	
Vettenranta K <i>et al</i> (21)  Case series	8	Neuroblastoma: n=5 Rhabdomyosarcoma: n=2 Burkitt's Lymphoma: n=1  Median Age: 4.5 yrs (2 months – 13 yrs)  All patients were heavily pre-treated with chemotherapy;  4/8 patients had failed previous mobilisation with CM + G-CSF ( <b>remobilisation group</b> );  One patient had also received local radiation	<b>Add-on plerixafor:</b> Cyclophosphamide 1-4g/m <sup>2</sup> plus G-CSF 10 mcg/kg (SC), then plerixafor 0.2-0.24mg/kg (1-3 doses): n=4  <b>Remobilisation:</b> G-CSF 10 mcg/kg (SC), then plerixafor 0.24 mcg/kg (1-3 doses): n=4	2/4 patients in add-on group achieved acceptable harvest (> 2 x 10 <sup>6</sup> CD34 <sup>+</sup> cell/kg)  4/4 patients in remobilisation group achieved acceptable harvest (> 2 x 10 <sup>6</sup> CD34 <sup>+</sup> cell/kg)  One patient relapsed following high dose chemotherapy otherwise authors considered plerixafor to be safe.	

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Study	No of patients	Baseline Characteristics	Intervention	Outcome	Comment
Hubel K <i>et al</i> (14)  Retrospective review of patients from 23 centres enrolled in the German plerixafor compassionate use program.	7	Various cancers (detail not provided)  Median Age: 12 (range not known)  All patients failed previous mobilisation or collection after G-CSF alone or G-CSF + Chemotherapy.	G-CSF 10 mcg/kg daily (SC) for 5 days;  Plerixafor 0.24mg/kg 11 hr before apheresis and on each day of apheresis up to a maximum of 7 injections.  2/7 children also received chemotherapy	Median CD34+ cell harvest 15.39 x 10 <sup>6</sup> cells/kg (range 1.49 – 29.53);  5/7 patients in total were eligible for and went on to have AHSCT (1/2 of the chemotherapy patients and 4/5 in the non-chemotherapy patients).  1 patient experienced abdominal pain and balance disorder. These were described as mild.	The original inclusion criterion was for patients aged 18 – 78 years. However, 7/60 patients enrolled were children and their results were reported separately; the median age of these children was not provided.
G-CSF = Granulocyte Colony Stimulating Factor; CM = Chemomobilisation (use of chemotherapy to stimulate stem cell mobilisation)					

### 4.2 Trials in progress

We searched clinicaltrials.gov and found two studies in paediatric patients with solid tumours:

- *A Combined Study in Pediatric Cancer Patients for Dose Ranging and Efficacy/Safety of Plerixafor Plus Standard Regimens for Mobilization versus Standard Regimens Alone.* This is a multi-site study of plerixafor in paediatric cancer patients. It will be conducted in two stages: a dose escalation study followed by an open-label, randomised, comparative study. Stage 2 will involve addition of plerixafor treatment prior to apheresis for those patients randomised to the plerixafor plus standard mobilisation treatment. Estimated completion date: June 2017 [[NCT01288573](#)].
- *Stem Cell Harvesting Using G-CSF Plus Plerixafor, in First -Line, for Heavily Pre-Treated Pediatric Oncology Patients.* This phase 4 study proposes to examine the applicability and feasibility of harvesting autologous stem cells by means of G-CSF plus plerixafor as the first-line intervention for paediatric patients with specific indications. The indications are not stated. This study is not yet recruiting [[NCT02006225](#)].

### 4.3 Evidence of cost-effectiveness

We found no studies on the cost-effectiveness of plerixafor as stimulant for PBSC mobilisation in children undergoing AHST for solid tumours.

### 4.4 Safety

Plerixafor is fairly well tolerated in adults. Common side effects include injection and infusion site reactions, nausea, diarrhoea, vomiting, and abdominal discomfort. It may also cause dizziness, headache and insomnia. Abnormal dreams and nightmares have also been reported. The safety profile in children is less well known as experience is more limited.

Most of the studies included in this review described plerixafor as well tolerated with side effects, usually gastrointestinal, being mild to moderate. Eight of 24 (25 percent) patients in the largest study experienced mild toxicity; diarrhoea (five patients), nausea (one patient), ossalgia (one patient) and urticaria (one patient).

Son *et al* reported significant psychiatric intolerances; four patients experienced nightmares nyctophobia and visual hallucinations. In one patient, visual hallucinations persisted for about a month.(20)

In the study reported by Hong *et al*, one patient died on day three, while two medulloblastoma patients developed serious lung problems and died of respiratory failure, although the pathogenesis was not understood.(13)

### 4.5 Summary of section 4

We found no systematic reviews or randomised studies on the clinical effectiveness of plerixafor used in combination with G-CSF in children undergoing PBST for solid tumours. We found one ongoing randomised study and one other study not yet recruiting.

We found twelve case series of children with solid tumours who received plerixafor added to G-CSF, either as pre-emptive or rescue mobilisation. Most of these involved very small numbers of patients.

In several case series reported, when plerixafor was added to steady-state G-CSF in children with solid tumours eligible for AHST who had failed previous mobilisation attempts with G-CSF or G-CSF plus chemomobilisation, it produced a successful CD34+ cell harvest (3.5 to 5 x 10<sup>6</sup> CD34+ cells/kg BW) in about 70 percent of patients. Many of these patients went on to have successful transplants. These results are unreliable because they are based on uncontrolled trials so the absolute effects of plerixafor are not

known. These small case series do not provide a true representation of efficacy, in that unsuccessful mobilisations may not be reported.

Plerixafor was fairly well tolerated in several of the studies included in this review. However, one of these studies revealed more severe and persistent psychiatric side effects, notably insomnia, nightmares and visual hallucination. In one study, three out of six children died within 11 days of receiving plerixafor, although the deaths were not confirmed as being related to plerixafor.

We found not studies on the cost-effectiveness of plerixafor for PBSC mobilisation in children undergoing AHST for solid tumours.

## 5 Discussion and conclusions

1. *Is plerixafor in stem cell mobilisation clinically effective in ensuring adequate stem cell mobilisation and a successful harvest in children with solid tumours where peripheral stem cell support (PBSCT) is a recognised treatment compared with no intervention or with other standardised treatments?*

We found no systematic reviews or controlled study evidence on the effects of plerixafor, used in combination with G-CSF, as PBSC mobilisation in children undergoing PBSCT for solid tumours. One randomised study is ongoing and another study is planned, but not yet recruiting.

Most of the supporting data are weak and based on case series reviews. Although they reported very high rates of successful mobilisation and stem cell harvest (50 to 100 percent of patients), the studies were uncontrolled, involved too few patients with too much heterogeneity in patient population to give a fair assessment of the efficacy of this approach. Being case series, they could have exaggerated the absolute effects of this treatment.

Limited data show that plerixafor may be an effective and safe agent for stem cell collection in paediatric patients with solid tumours, but proper randomised comparative studies are required to address its efficacy and safety.

Plerixafor appeared to be fairly well tolerated in most of the studies. However, psychiatric side effects were higher than expected in one of these studies. Until more is known from prospective controlled trials, plerixafor should be used with caution in children.

2. *Is plerixafor in stem cell mobilisation cost effective in children with solid tumours where PBSCT is a recognised treatment?*

We found no studies on the cost-effectiveness of plerixafor in children undergoing PBSCT for solid tumours.

### **Competing Interest**

All SPH authors have completed the ICMJE uniform disclosure form ([www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf)) and declare: grants from NHS England to SPH to undertake the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

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## 7 Search Strategy

Population, Intervention, Comparator and Outcomes (PICO)

Population	Intervention	Comparator	Outcomes	Studies
Children with solid tumours where PBSCT is a recognised treatment	Plerixafor in stem cell mobilisation in combination with G-CSF	No intervention  Any other standardised treatments including: <ul style="list-style-type: none"> <li>Granulocyte Colony Stimulating factors (G-CSF)</li> <li>Chemomobilisation along with G-CSF</li> </ul>	Any, including: <ul style="list-style-type: none"> <li>Survival</li> <li>Successful harvest</li> <li>Successful PBSCT</li> <li>cost-effectiveness</li> <li>Quality of life</li> <li>Safety/Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>Meta-analyses</li> <li>Systematic reviews</li> <li>Randomised controlled trials</li> <li>Prospective non-randomised clinical study</li> <li>Other clinical study</li> <li>Health economics studies</li> </ul>

**Search date:** 3 August 2015

**Databases searched:** PubMed, Embase, Cochrane, TRIP and NICE Evidence search, limiting to English language studies.

- 1 plerixafor/
- 2 (plerixafor or mozobil).ti,ab.
- 3 1 or 2
- 4 granulocyte colony stimulating factor/
- 5 stem cell mobilization/
- 6 (gcsf or g-csf or "granulocyte csf" or granulocyte colony stimulating factor\*).ti,ab.
- 7 ((hematopoietic or haematopoietic or stem cell\*) adj5 (mobili\* or stimulat\* or collect\*)).ti,ab.
- 8 4 or 5 or 6 or 7
- 9 juvenile/ or adolescent/
- 10 child/ or boy/ or girl/ or infant/ or preschool child/ or school child/ or toddler/
- 11 (infant? or baby or babies or child\* or schoolchild\* or preschool\* or toddler? or girl? or boy? or pediatric\* or paediatric\* or teen\* or adolescen\* or youth\*).ti,ab.
- 12 9 or 10 or 11
- 13 3 and 8 and 12
- 14 ((plerixafor or mozobil) and (infant? or baby or babies or child\* or schoolchild\* or preschool\* or toddler? or girl? or boy? or pediatric\* or paediatric\* or teen\* or adolescen\* or youth\*)).ti.
- 15 13 or 14