NHS England

Evidence review: 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

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Prepared by: The NICE Medicines and Technologies Programme on behalf of NHS England Specialised Commissioning

The content of this evidence review was up-to-date in June 2019. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Key points

Regulatory status: Plerixafor is used to help dislodge or 'mobilise' stem cells from the bone marrow so they can be released into the blood. Using 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 (HSCT) is an 'off label' use of this medicine. Plerixafor received a marketing authorisation in July 2009 for use in combination with granulocyte-colony stimulating factor (G-CSF) to enhance mobilisation of stem cells for subsequent autologous HSCT in adults with lymphoma and multiple myeloma whose cells mobilise poorly.

Overview

Autologous HSCT is used to treat various haematological and non-haematological disorders. In autologous transplants, stem cells are removed from a person, stored, and later given back to that same person, rather than using a stem cell donor. Before HSCT is undertaken, 'mobilisation' is needed to dislodge the stem cells from the bone marrow and increase the number of peripheral blood stem cells (PBSC) in the circulating blood flow. The circulating PBSC can then be collected in a procedure called apheresis.

For mobilisation, intravenous chemotherapy and a growth factor (G-CSF) are usually given. However, insufficient cells are collected for autologous transplant in about 10–20% of cases. Plerixafor can be used with G-CSF to increase the amount of PBSC collected. Using plerixafor after unsuccessful PBSC collection is known as **rescue treatment**. Plerixafor has also been used after G-CSF (with or without chemotherapy) in people with a low level of circulating PBSC in the blood on the day of collection. This is known as **pre-emptive treatment**.

NHS England commissions plerixafor for specific haematological cancers (multiple myeloma and lymphoma) in people of any age, and non-haematological solid tumours in people aged 24 years or under. This evidence review considers the effectiveness and safety of plerixafor as a rescue or pre-emptive treatment in stem cell mobilisation for people of any age with haematological tumours (apart from multiple myeloma and lymphoma) or haematological paraneoplastic complications who are receiving autologous HSCT. A related evidence review considers plerixafor as a rescue or pre-emptive in stem cell mobilisation for people aged over 24 years with non-haematological solid tumours.

This evidence review includes 1 retrospective case series, Lee et al. (2014), which investigated 2 men and 1 woman with amyloid light-chain (AL) amyloidosis with cardiac involvement. In this study, successful mobilisation of cells from the bone marrow was defined as a harvest of 2.5 to 5.0 million CD34+ cells/kg after treatment with G-CSF and rescue plerixafor. CD34+ is the protein expressed on the PBSCs that can be detected and measured, allowing the number of stem cells in the blood or the harvest to be counted.

In Lee et al. (2014) a median of 5.7 million CD34+ cells/kg were collected in a median of 2 days. All 3 participants met the threshold for successful mobilisation of cells and all 3 proceeded to HSCT. Neutrophil and platelet engraftment took place in all participants (within 12 days for neutrophils and within 16 days for platelets).

Several grade III and IV toxicities were reported but the authors suspected that these were due to underlying amyloidosis and complications of high-dose chemotherapy, neutropenia and immunosuppression, rather than plerixafor.

The study in this evidence review is a small, retrospective case series which is subject to bias and confounding and has many limitations affecting the application of the findings to clinical practice. The dosing regimen used in the study was consistent with the dosing regimen for the licensed indications for plerixafor, and it was used in combination with G-CSF. While all 3 of the people in the study achieved a successful mobilisation of cells and were able to proceed to HSCT, this provides very limited evidence on the clinical effectiveness and safety of using plerixafor as a rescue treatment for inducing stem cell mobilisation in people with AL amyloidosis. It does not provide any information on the efficacy or safety of plerixafor in haematological tumours or other paraneoplastic complications. It also does not provide any information about the efficacy or safety of plerixafor when used as a pre-emptive treatment in this population or in people older than 60 years or in children or young people. No evidence was found to determine whether plerixafor is cost-effective for stem cell mobilisation in haematological tumours.

Contents

1. Introduction

Background and current guidance

Haematopoietic stem cell transplantation (HSCT), also known as blood and marrow transplantation, is used to treat various haematological and non-haematological disorders. It is broadly divided into 2 main types: allogeneic and autologous transplantation.

Allogeneic HSCT involves replacing a person's bone marrow stem cells with stem cells from a donor. Autologous transplantation uses the person's own peripheral blood stem cells (PBSCs), which are harvested before high-dose chemotherapy is administered. It enables the person to be treated with higher doses of chemotherapy than would be possible without subsequent replacement of the harvested stem cells, because the chemotherapy destroys the person's remaining stem cell tissue.

Before an autologous transplant is undertaken, 'mobilisation' is needed to dislodge the haematopoietic stem cells from the bone marrow and increase the number of PBSC in the circulating blood flow. The circulating PBSC can then be collected using a cell separator in a procedure called apheresis. For mobilisation, intravenous chemotherapy and a growth factor called granulocyte-colony stimulating factor (G-CSF) are usually given. This results in successful mobilisation and collection of PBSC in about 80% of people. However, insufficient cells are collected for autologous transplant in about 10–20% of cases. These people are usually offered a second round of stem cell mobilisation and collection using a more intensive chemotherapy regimen. This needs another inpatient admission with more chemotherapy and G-CSF, and has associated adverse effects and costs. Additional attempts at mobilisation are effective only in a small proportion of people (up to 20%). Mobilisation in children can be particularly challenging because of the intensity of chemoradiotherapy regimes given earlier in the treatment pathway, and the increasing use of sequential high-dose therapy.

Plerixafor can be used with G-CSF to increase the amount of PBSC collected (Mozobil summary of product characteristics). In some conditions (such as lymphoma and multiple myeloma), this treatment has been shown to mobilise PBSC in up to 80% of people who previously failed to collect enough cells. Using plerixafor after unsuccessful PBSC collection is known as rescue treatment.

Plerixafor has also been used after chemotherapy and G-CSF in people with a low level of circulating PBSC in the blood on the day of collection. This is known as pre-emptive treatment. Pre-emptive treatment with plerixafor can improve the number of stem cells mobilising into the blood, avoid a failure of stem cell harvesting, and prevent a second attempt at mobilisation.

NHS England commissions plerixafor for specific haematological cancers (multiple myeloma and lymphoma) in people of any age, and non-haematological solid tumours in people aged 24 years or under. This evidence review considers the effectiveness and safety of plerixafor as a rescue or pre-emptive treatment in stem cell mobilisation for people of any age with haematological tumours (apart from multiple myeloma and lymphoma) or haematological paraneoplastic complications (such as amyloidosis). This review considers people who can be treated with autologous HSCT, who have received either chemotherapy plus G-CSF or

G-CSF alone and who have a low peripheral blood CD34+ cell count. A related evidence review considers plerixafor as a rescue or pre-emptive in stem cell mobilisation for people aged more than 24 years with non-haematological solid tumours.

See the NHS England clinical commissioning policies on HSCT and plerixafor for stem cell mobilisation for more information.

Product overview

Mode of action

Plerixafor is used to help dislodge or 'mobilise' the stem cells from the bone marrow so they can be released into the blood. It works by blocking the activity of a protein called the CXCR4 chemokine receptor. This protein normally helps to keep stem cells within the bone marrow. By blocking its activity, plerixafor allows the stem cells to be released into the blood, so that they can be collected (Mozobil European public assessment report).

Regulatory status

Plerixafor received a marketing authorisation in July 2009. It is licensed for use in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in adults with lymphoma and multiple myeloma whose cells mobilise poorly (Mozobil summary of product characteristics).

Age over 60 years and/or prior myelosuppressive chemotherapy and/or extensive prior chemotherapy and/or a peak circulating stem cell count of less than 20 stem cells/microlitre, have been identified as predictors of poor mobilisation (Mozobil summary of product characteristics).

Using plerixafor for other indications (including the indications covered by the existing NHS England clinical commissioning policy on plerixafor for stem cell mobilisation and the indications considered in this evidence review) is an 'off label' use of this medicine. In line with the guidance from the General Medical Council (GMC) on prescribing unlicensed medicines, the prescriber should take full responsibility for determining the needs of the person and whether using plerixafor is appropriate outside its authorised indications. Supporting information and advice is also available from the GMC.

Dosing information

Plerixafor is a solution for subcutaneous injection. G-CSF is used on its own for 4 days before plerixafor is added. Plerixafor is administered 6–11 hours before each apheresis session (when blood is taken and the stem cells are extracted and frozen). It has commonly been used in clinical trials for 2 to 4 (and up to 7) consecutive days. Depending on body weight, the recommended dose of plerixafor for the licensed indications is:

- 20 mg fixed dose or 0.24 mg/kg for people weighing 83 kg or less, and
- 0.24 mg/kg for people weighing more than 83 kg.

The maximum dosage should not exceed 40mg/day.

In the study included in this evidence review, a dose of 0.24 mg/kg per day was used. The authors reported that a dose adjustment for creatinine clearance was made but did not report what dose was used and in which patients.

In renal impairment (creatinine clearance 20 to 50 ml/min), the dose should be reduced by one-third to 0.16 mg/kg per day and should not exceed 27 mg/day. However, clinical data with this dose adjustment are limited.

2. Methodology

A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) for this review was provided by NHS England's Policy Working Group for the topic (see the literature search terms section for more information). The research questions for this evidence review are:

1. In people of any age with haematological tumours (apart from multiple myeloma and lymphoma) or haematological paraneoplastic complications that can be treated with HSCT and who are scheduled for autologous HSCT, what is the clinical effectiveness of plerixafor in stem cell mobilisation compared to standard care?
2. In people of any age with haematological tumours (apart from multiple myeloma and lymphoma) or haematological paraneoplastic complications that can be treated with HSCT and who are scheduled for autologous HSCT, what is the safety of plerixafor in stem cell mobilisation compared to standard care?
3. In people of any age with haematological tumours (apart from multiple myeloma and lymphoma) or haematological paraneoplastic complications that can be treated with HSCT and who are scheduled for autologous HSCT, what is the cost-effectiveness of plerixafor in stem cell mobilisation compared to standard care?
4. From the evidence selected, are there any subgroups of people who would gain greater benefit or harm from treatment with plerixafor, in particular:
    a. rescue or pre-emptive treatment in stem cell mobilisation
    b. effects in children (0 to 18 years) and adults (over 18 years).

The searches for evidence to support the use of plerixafor for stem cell mobilisation in people of any age with haematological tumours (apart from multiple myeloma and lymphoma) or haematological paraneoplastic complications were undertaken by the NICE Guidance Information Services' team. Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the PICO. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the PICO inclusion criteria for this evidence review. More information can be found in the sections on search strategy and evidence selection.

The NICE evidence summary: process guide (2017) sets out the how the summaries are developed and approved for publication. The included studies are quality assessed using the National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework as set out in NHS England's Guidance on conducting evidence reviews for Specialised Services Commissioning Products (2016) (see the grade of evidence section for more information).

3. Summary of included studies

One case series identified from the evidence search (Lee et al. 2014) was included in this evidence summary.

A summary of the included study is shown in table 1 (see the evidence summary tables for full details).

Table 1 Summary of included study

Study	Population	Intervention and comparison	Primary outcome
Lee et al. 2014 Uncontrolled retrospective case series of 5 people in the US.	All participants had AL amyloidosis with cardiac involvement. Two people received upfront plerixafor and 3 people received rescue plerixafor. The individual characteristics of the 3 people who had rescue treatment with plerixafor, and met the inclusion criteria, are described below: Person 1: A 57-year-old man with cardiac, renal and peripheral nerve involvement. Previous orthotopic heart transplantation. PBSC yield before rescue treatment with plerixafor: 0.54 x10^6/kg. Person 2: A 56-year-old man with cardiac, liver and soft-tissue involvement. Previous diagnosis of smouldering myeloma 7 years before. PBSC yield before rescue treatment with plerixafor: 1.1 x10^6/kg.	In the 3 participants included in this evidence review, plerixafor was given after inadequate response to G-CSF. G-CSF was administered on days 1 to 3 at a dose of 16 micrograms/kg. After the decision to add plerixafor was made, the dose of G-CSF was reduced to 10 micrograms/kg and plerixafor was given at 0.24 mg/kg in the evening with an additional dose of G-CSF of 10 micrograms/kg the next morning until the target CD34+ cell yield was achieved. No comparator	Number of CD34+ cells collected

	Person 3: A 45-year-old woman with cardiac involvement. PBSC yield before rescue treatment with plerixafor: 0.9 x10^6/kg.		
Abbreviations: PBSC, peripheral blood stem cell; G-CSF, granulocyte-colony stimulating factor			

Details of the excluded studies are listed in the section on evidence selection.

4. Results

An overview of the results for clinical effectiveness and safety and tolerability can be found in the evidence summary table. The research questions for the evidence review and the key outcomes identified in the scope are discussed in this section.

The grade of evidence for all outcomes is C.

1. In people of any age with haematological tumours (apart from multiple myeloma and lymphoma) or haematological paraneoplastic complications that can be treated with HSCT and who are scheduled for autologous HSCT, what is the clinical effectiveness of plerixafor in stem cell mobilisation compared to standard care? Stem cell mobilisation

In the 3 participants who did not achieve a PBSC yield of ≥1.5 million CD34+ cells/kg with G-CSF alone, rescue plerixafor was added until the target CD34+ cell count of 2.5 to 5.0 million cells/kg was achieved. The total PBSC yield in these 3 participants was 2.9, 5.7, and 5.9 million cells/kg over 3, 2, and 2 days respectively.

Autologous haematopoietic stem cell transplantation (HSCT)

All 3 participants who received rescue plerixafor and achieved a target CD34+ cell count yield of 2.5 to 5.0 million cells/kg proceeded to autologous HSCT.

Neutrophil and platelet engraftment

Neutrophil engraftment occurred at a median of 11 days (range 9 to 12 days) and platelet engraftment occurred at a median of 13 days (range 12 to 16 days). Neutrophil and platelet engraftment occurred in all 3 participants who received plerixafor as rescue treatment (within 12 days for neutrophils and 16 days for platelets).

2. In people of any age with haematological tumours (apart from multiple myeloma and lymphoma) or haematological paraneoplastic complications that can be treated with HSCT and who are scheduled for autologous HSCT, what is the safety of plerixafor in stem cell mobilisation compared to standard care?

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. Adverse events and deaths were categorised according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

One participant who had rescue plerixafor died 224 days after transplant from large bowel obstruction and septic shock.

Summary of product characteristics

According to the plerixafor summary of product characteristics, very common adverse effects seen in at least 1 in 10 people in studies of lymphoma and multiple myeloma are diarrhoea, nausea and injection site reactions. Common adverse effects (in between 1 in 100 and 1 in 10 people) are insomnia, dizziness, headache, vomiting, abdominal pain, stomach discomfort, dyspepsia, abdominal distention, constipation, flatulence, oral hypoaesthesia (reduced sense of touch or sensation), dry mouth, hyperhidrosis, erythema, arthralgia, musculoskeletal pain, fatigue and malaise.

3. In people of any age with haematological tumours (apart from multiple myeloma and lymphoma) or haematological paraneoplastic complications that can be treated with HSCT and who are scheduled for autologous HSCT, what is the cost-effectiveness of plerixafor in stem cell mobilisation compared to standard care?

No evidence was found to determine whether plerixafor is cost-effective for treating people with haematologic tumours or haematological paraneoplastic complications who are receiving autologous HSCT.

5. Discussion

Evidence strengths and limitations

The evidence presented in this review is based on data from 1 retrospective review of electronic medical records in 1 centre in the US. Retrospective case series are subject to bias and confounding and rely on accurate and complete data recording. While all 3 of the people in the study achieved a successful mobilisation of cells and were able to proceed to HSCT, this study provides very limited evidence on the clinical effectiveness, safety and cost-effectiveness of plerixafor for inducing stem cell mobilisation in people with haematological tumours or other haematological paraneoplastic complications. It also provides no data comparing plerixafor with any other treatments for stem cell mobilisation. No statistical analyses were reported. This type of study cannot reliably answer the research questions: the results can only be considered hypothesis generating and cannot support any definitive conclusions.

The study focused on people with AL amyloidosis with cardiac involvement only. Therefore, the findings may not be applicable to people with haematological tumours or other haematological paraneoplastic complications. As the ages of the participants in the study were 45 to 57 years, the findings may not be applicable to people over 60 years, a known predictor of poor mobilisation. The findings may also not be applicable to children, in whom

mobilisation can be particularly challenging. The 3 people included in the study received plerixafor as a rescue treatment. Therefore, the available evidence does not provide information of the efficacy and safety of using plerixafor as a pre-emptive treatment in people with haematological tumours or other haematological paraneoplastic complications.

Other treatments

No other treatments are generally considered at the same stage in the management pathway for stem cell mobilisation in people with haematological tumours.

6. Conclusion

Stem cell mobilisation is needed before an autologous transplant is undertaken to dislodge the haematopoietic stem cells from the bone marrow and increase the number of PBSC in the circulating blood flow. In adults with lymphoma and multiple myeloma, plerixafor can be used to help dislodge or 'mobilise' the stem cells from the bone marrow so they can be released into the blood and collected.

This evidence review includes a case series of 5 people with AL amyloidosis with cardiac involvement. Three people, aged between 45 and 57 years, met the PICO and received plerixafor as rescue treatment. Before rescue treatment with plerixafor, all 3 participants had an inadequate CD34+ yield with G-CSF alone. The study included in this evidence review, although small, uncontrolled and low quality, demonstrated that in 3 people the PBSC yield was increased after rescue treatment with plerixafor, and all proceeded to HSCT.

From the study included in this evidence review, no adverse events were reported as being attributable to plerixafor. However, reporting may have been incomplete due to its design. Because of the small size of the study, and the concomitant treatment with G-CSF, it is not possible to draw firm conclusions on the safety of plerixafor in people with haematological tumours or haematological paraneoplastic complications. It is likely that the plerixafor summary of product characteristics provides the best overview of the adverse effects profile of plerixafor, even for indications outside of the terms of the license.

This study provides very limited evidence on the clinical effectiveness and safety of plerixafor as rescue treatment for stem cell mobilisation in people with AL amyloidosis. It does not provide any information on the efficacy or safety of plerixafor in haematological tumours or other paraneoplastic complications. It also does not provide any information about the efficacy or safety of plerixafor when used as a pre-emptive treatment in this population or in people older than 60 years or in children or young people.

7. Evidence summary table

Use of plerixafor to induce mobilisation of PBSC in people with AL amyloidosis and cardiac involvement							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
Study reference 1: Lee et al. 2014							
P1 retrospective case series of 5 people in the US	All participants had AL amyloidosis with cardiac involvement. The individual characteristics of the 3 people who had rescue treatment with plerixafor are described below: Person 1: A 57-year-old man with cardiac, renal and peripheral nerve involvement. Previous orthotopic heart transplantation. PBSC yield before rescue treatment with plerixafor: 0.54 x10^6/kg. Person 2: A 56-year-old man with	Two people received upfront plerixafor in combination with G-CSF and 3 people received rescue plerixafor after inadequate mobilisation with G-CSF alone. In the 3 participants included in this evidence review, plerixafor was given after inadequate response to G-CSF. G-CSF was administered on days 1 to 3 at a dose of 16 micrograms/kg. After the decision to add plerixafor was made, the dose of G-CSF was reduced to 10 micrograms/kg and plerixafor was given at 0.24 mg/kg in the evening with an additional dose of G-CSF of 10 micrograms/kg the next morning until the target CD34+ cell yield was achieved	Clinical effectiveness	Number of CD34+ cells collected	Person 1: 2.9 x 10^6 cells/kg Person 2: 5.9 x 10^6 cells/kg Person 5: 5.7 x 10^6 cells/kg	Poor quality study (3/10 or less). Limited evidence in 3 people from a single centre in the US. Retrospective review of electronic medical records with no comparator arm.	Direct study focusing on people with AL amyloidosis and the characteristics of interest. It is unclear how generalisable the results will be to people with haematological tumours, to other age groups and to a UK population.
			Clinical effectiveness	Number of participants collecting 2.5 to 5.0 x 10^6 CD34+ cells/kg	3/3 (100%)		
			Clinical effectiveness	Number of days of apheresis	Person 1: 3 days Person 2: 2 days Person 5: 2 days		
			Clinical effectiveness	Number of participants proceeding to HSCT	3/3 (100%)		
			Clinical effectiveness	Number of days to neutrophil engraftment	Person 1: 12 days Person 2: 11 days Person 5: 9 days		

Use of plerixafor to induce mobilisation of PBSC in people with AL amyloidosis and cardiac involvement							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
	cardiac, liver and soft-tissue involvement. Previous diagnosis of smouldering myeloma 7 years before. PBSC yield before rescue treatment with plerixafor: 1.1 x10^6/kg. Person 5: A 45-year-old woman with cardiac involvement. PBSC yield before rescue treatment with plerixafor: 0.9 x10^6/kg.		Clinical effectiveness	Number of days to platelet engraftment	Person 1: 16 days Person 2: 13 days Person 5: 12 days		
			Safety	Death	Person 2: Died at day 224 from large bowel obstruction and septic shock.		
			Safety	Grade III to IV toxicities	Person 1: Sepsis, renal, hyperglycaemia Person 2: Not reported Person 5: Hepatic (bilirubin)		
			Safety	Adverse events attributed to plerixafor	0/3 (0%)		
Critical appraisal summary See section 3.5.2.1 Very small, uncontrolled, retrospective observational study at high risk of bias and confounding. Included people with AL amyloidosis with cardiac involvement only and the age range of people in the study was 45 to 57 years. Therefore, the findings may not be applicable to people with haematological tumours, people aged over 60 years (a known predictor of poor mobilisation) or to children (in whom mobilisation can be particularly challenging).							
Abbreviations: G-CSF; Granulocyte-colony-stimulating factor, HSCT; haematopoietic stem cell transplantation.							

8. Grade of evidence table

Use of plerixafor to induce mobilisation of PBSC in people with AL amyloidosis and cardiac involvement					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Median number of CD34+ cells collected	Lee et al. 2014	3/10	Direct	C	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 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 10^6 cells/kg (range 2.9 to 5.9 x 10^6 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 10^6 cells/kg (range 0.54 to 1.1 x 10^6 cells/kg). 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.
Number of participants collecting 2.5 to 5.0 x 10^6 CD34+ cells/kg	Lee et al. 2014	3/10	Direct	C	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 above for limitations.

Number of days of apheresis	Lee et al. 2014	3/10	Direct	C	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 above for limitations.
Number of participants proceeding to transplant	Lee et al. 2014	3/10	Direct	C	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 above for limitations.
Number of days to neutrophil engraftment	Lee et al. 2014	3/10	Direct	C	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 above for limitations.
Number of days to platelet engraftment	Lee et al. 2014	3/10	Direct	C	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 above for limitations.
Death	Lee et al. 2014	3/10	Direct	C	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 above for limitations.
Grade III/IV toxicities	Lee et al. 2014	3/10	Direct	C	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 above for limitations.
Adverse events attributable to plerixafor	Lee et al. 2014	3/10	Direct	C	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. See above for limitations.
Abbreviations: G-CSF; Granulocyte-colony-stimulating factor, HSCT; haematopoietic stem cell transplantation, PBSC; peripheral blood stem cell					

9. Literature search terms

P –Population and Indication	Patients of any age with haematological tumours other than multiple myeloma and lymphoma (e.g. aPML, CLL, myelofibrosis) OR haematological paraneoplastic complications (amyloidosis),

Describe the relevant population and indication provided previously including if necessary disease severity or duration, previous treatment, new or recurrent symptoms, any specific co-morbidities and other population factors (for example, age range). Add details of any subgroups or stratifications for which separate evidence may be required.	that can be treated with autologous HSCT, who have received either chemotherapy + G-CSF or G-CSF alone and who have a low peripheral blood CD34+ cell count. [Subgroups of interest: children OR adults] [effects in children (0-18 years) and adults (>18 years)]
I – Intervention Describe the intervention details provided previously including if necessary details of treatment, mode of delivery, size/frequency/duration of dose, position of intervention in treatment pathway (e.g. first/second line/salvage) and any background / concomitant medication	Plerixafor (as EITHER a rescue OR pre-emptive treatment) [Subgroups of interest: a rescue OR pre-emptive treatment]
C – Comparators What is/are the main alternative/s to compare with the intervention being considered? Describe the comparator details provided previously including if necessary details of treatment, mode of delivery, size/frequency/duration of dose, position of intervention in treatment pathway (e.g. first/second line/salvage) and any background / concomitant medication	No plerixafor treatment A further round of G-CSF +/- chemotherapy

O – Outcomes
 	
Outcomes should be patient focused and relate to those detailed in the PPP and the Research Questions covering
	Critical to decision-making:
	
	• clinical effectiveness, for example:
	  ○ number of patients collecting sufficient stem cells to be eligible for transplant
	  ○ total CD34+cell count (x10^6/kg) in harvest of patients receiving plerixafor

clinical effectiveness, safety and cost-effectiveness as required. Examples will be topic specific but might include intermediate or short-term outcomes; mortality; morbidity; quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	○ number of patients meeting target peripheral blood CD34+ thresholds and proceeding to apheresis ○ number of days of apheresis ○ number of patients proceeding to transplant ○ median number of days to neutrophil and platelet engraftment • adverse effects of plerixafor • mortality *Important to decision-making:* cost-effectiveness of plerixafor
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2009-2019
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters and editorials

Study design	Case reports, resource utilisation studies
Abbreviations: G-CSF; Granulocyte-colony stimulating factor: HSCT; Haematopoietic stem cell transplantation	

10. Search strategy

Database search strategies

Database: Medline
Platform: Ovid
Version: 1946 to March 18 2019
Search date: 19/03/2019
Number of results retrieved: 361
Search strategy:
1 (plerixafor* or amd 3100 or amd3100 or mozobil* or jm 3100 or jm3100 or sdzsid 791 or sdzsid791 or sid 791 or sid791).tw. (1477)
2 Hematopoietic Stem Cell Mobilization/ (3956)
3 Hematopoietic Stem Cell Transplantation/ (37906)
4 Hematopoietic Stem Cells/ (40574)
5 ((autologous or autogenous or autogeneic) adj2 stem* adj2 (mobilization or mobilisation*)).tw. (65)
6 (auto-sct or autosct).tw. (320)
7 (hematopoietic adj2 stem* adj2 (mobilization or mobilisation*)).tw. (362)
8 2 or 3 or 5 or 6 or 7 (40589)
9 1 and 8 (458)
10 animals/ not humans/ (4524962)
11 9 not 10 (387)
12 limit 11 to ed=20090101-20190321 (361)

Database: Medline in-process
Platform: Ovid
Version: 1946 to March 18 2019
Search date: 19/03/2019
Number of results retrieved: 5
Search strategy: see Medline above

Database: Medline epubs ahead of print
Platform: Ovid
Version: March 18, 2019
Search date: 19/03/2019
Number of results retrieved: 6
Search strategy: see Medline above

Database: Medline daily update
Platform: Ovid
Version: March 2018
Search date: 19/03/2019
Number of results retrieved: 1
Search strategy see Medline above

Database: Embase
Platform: Ovid
Version: 1980 to 2019 Week 11
Search date: 19/03/2019
Number of results retrieved: 703
Search strategy:

1 Plerixafor/ (4463)

2 (plerixafor* or amd 3100 or amd3100 or mozobil* or jm 3100 or jm3100 or sdzsid 791 or sdzsid791 or sid 791 or sid791).tw. (4675)
3 1 or 2 (5339)
4 stem cell mobilization/ (7055)
5 Hematopoietic Stem Cell Transplantation/ (34977)
6 Hematopoietic Stem Cell/ (54231)
7 ((autologous or autogenous or autogeneic) adj2 stem* adj2 (mobilization or mobilisation*)).tw. (199)
8 (auto-sct or autosct).tw. (1129)
9 (hematopoietic adj2 stem* adj2 (mobilization or mobilisation*)).tw. (711)
10 4 or 5 or 6 or 7 or 8 or 9 (91815)
11 3 and 10 (1915)
12 nonhuman/ not (human/ and nonhuman/) (4321121)
13 11 not 12 (1724)
14 limit 13 to dc=20090101-20190321 (1621)
15 limit 14 to english language (1601)
16 (letter or editorial).pt. (1599576)
17 (conference abstract or conference paper or conference proceeding or "conference review").pt. (4067509)
18 16 or 17 (5667085)
19 15 not 18 (703)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL
Platform: Wiley
Version:
CDSR – Issue 3 of 12, March 2019
CENTRAL – Issue 3 of 12, March 2019
Search date: 19/03/2019
Number of results retrieved:
CDSR – 1
CENTRAL – 37.

#1 MeSH descriptor: [Hematopoietic Stem Cell Mobilization] this term only 287
#2 MeSH descriptor: [Hematopoietic Stem Cell Transplantation] this term only 1086
#3 MeSH descriptor: [Hematopoietic Stem Cells] this term only 269
#4 ((((autologous or autogenous or autogeneic) Near/2 stem* Near/2 (mobilization or mobilisation*)))):ti,ab,kw 22
#5 (((auto-sct or autosct))):ti,ab,kw 77
#6 (((hematopoietic Near/2 stem* Near/2 (mobilization or mobilisation*)))):ti,ab,kw 318
#7 (plerixafor* or amd 3100 or amd3100 or mozobil* or jm 3100 or jm3100 or sdzsid 791 or sdzsid791 or sid 791 or sid791):ti,ab,kw 134
#8 #1 or #2 or #3 or #4 or #5 or #6 1515
#9 #7 and #8 37

Database: HTA
Platform: CRD
Version: From 31 March 2018, the HTA database remains available, but CRD are no longer adding new records to it
Search date: 19/03/2019
Number of results retrieved: 6
Search strategy: plerixafor* or amd 3100 or amd3100 or mozobil* or jm 3100 or sdzsid 791or sid 791

Trials registry search results

Clinicaltrials.gov
Search date: 12 March 2019
Number of results retrieved: 75
Search strategy: Plerixafor or Mozibil AND stem cell

11. Evidence selection

A single literature search was conducted for 2 related evidence summaries looking at plerixafor for mobilisation in people receiving autologous HSCT for solid tumours or haematological tumours (excluding multiple myeloma and lymphoma) and haematological paraneoplastic complications. The search identified 797 references after duplicates were removed (see search strategy for full details). These references were screened using their titles and abstracts and 85 references were obtained and assessed for relevance. Of these, 1 reference is included in this evidence summary on haematological tumours and haematological paraneoplastic complications, and 2 references are included in the evidence summary on solid tumours. The remaining 82 references were excluded and are listed in the following table.

Study	Reason for exclusion
Aabideen, Kanakkande, Anoop, Parameswaran, Ethell, Mark E. et al. (2011) The feasibility of plerixafor as a second-line stem cell mobilizing agent in children. Journal of pediatric hematology/oncology 33(1): 65-7	Study includes children with solid tumours
Abhyankar, S., DeJarnette, S., Aljitawi, O. et al. (2012) A risk-based approach to optimize autologous hematopoietic stem cell (HSC) collection with the use of plerixafor. Bone marrow transplantation 47(4): 483-7	Study includes population with MM and/or lymphoma
Abusin, G. A., Abu-Arja, R. F., Gingrich, R. D. et al. (2013) An algorithm for utilizing peripheral blood CD34 count as a predictor of the need for plerixafor in autologous stem cell mobilization - Cost-effectiveness analysis. Journal of Clinical Apheresis 28(4): 293-300	Study combines various populations
Avramova, Boryana E., Yordanova, Maya N., Konstantinov, Dobrin N. et al. (2011) Successful mobilization of peripheral blood stem cells in children with cancer using plerixafor (Mozobil) and granulocyte-colony stimulating factor. Drug design, development and therapy 5: 407-9	Study includes children with solid tumours
Azar, Nabih, Ouzegdouh, Maya, Choquet, Sylvain et al. (2018) Impact of plerixafor (mozobil) on hospital efficiency: A single center experience. Journal of clinical apheresis 33(1): 5-13	Study combines various populations

Study	Reason for exclusion
Baertsch, M. A., Kriegsmann, K., Pavel, P. et al. (2018) Platelet Count before Peripheral Blood Stem Cell Mobilization Is Associated with the Need for Plerixafor But Not with the Collection Result. Transfusion Medicine and Hemotherapy 45(1): 24-31	Study combines various populations
Basak, G. W., Mikala, G., Koristek, Z. et al. (2011) Plerixafor to rescue failing chemotherapy-based stem cell mobilization: It's not too late. Leukemia and Lymphoma 52(9): 1711-1719	Study includes population with MM and/or lymphoma
Basak, Grzegorz W., Jaksic, Ozren, Koristek, Zdenek et al. (2011) Identification of prognostic factors for plerixafor-based hematopoietic stem cell mobilization. American journal of hematology 86(7): 550-3	Study includes population with MM and/or lymphoma
Bitan, Menachem, Eshel, Rinat, Sadot, Efraim et al. (2016) Combined plerixafor and granulocyte colony-stimulating factor for harvesting high-dose hematopoietic stem cells: Possible niche for plerixafor use in pediatric patients. Pediatric transplantation 20(4): 565-71	Study includes children with solid tumours
Boulad, F., Shore, T., van Besien, K. et al. (2018) Safety and efficacy of plerixafor dose escalation for the mobilization of cd34+ hematopoietic progenitor cells in patients with sickle cell disease: Interim results. Haematologica 103(5): 770-777	Does not contain a population of people undergoing autologous HSCT treated with plerixafor
Cappellari, Roberta, D'Anna, Marianna, Avogaro, Angelo et al. (2016) Plerixafor improves the endothelial health balance. The effect of diabetes analysed by polychromatic flow cytometry. Atherosclerosis 251: 373-380	Not a relevant study design
Cardenoux, Charlotte, Demeocq, Francois, Kanold, Justyna et al. (2010) Pegfilgrastim plus AMD 3100 for stem-cell mobilization in children. Pediatric blood & cancer 55(4): 769	Not a relevant study design
Chambon, Fanny, Merlin, Etienne, Rochette, Emmanuelle et al. (2013) Mobilization of hematopoietic stem cells by plerixafor alone in children: a sequential Bayesian trial. Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis 49(3): 453-8	Study includes children with solid tumours
Chen, A. I., Bains, T., Murray, S. et al. (2012) Clinical experience with a simple algorithm for plerixafor utilization in autologous stem cell mobilization. Bone marrow transplantation 47(12): 1526-9	Study combines various populations

Study	Reason for exclusion
De Blasio, Angelo, Rossi, Luigi, Zappone, Elisabetta et al. (2013) Plerixafor and autologous stem cell transplantation: impressive result in a chemoresistant testicular cancer patient treated with high-dose chemotherapy. Anti-cancer drugs 24(6): 653-7	Not a relevant study design
de Greef, G. E., Braakman, E., van der Holt, B. et al. (2019) The feasibility and efficacy of subcutaneous plerixafor for mobilization of peripheral blood stem cells in allogeneic HLA-identical sibling donors: results of the HOVON-107 study. Transfusion 59(1): 316-324	Does not contain a population of people undergoing autologous HSCT treated with plerixafor
Dhakal, B., D'Souza, A., Arce-Lara, C. et al. (2015) Superior efficacy but higher cost of plerixafor and abbreviated-course G-CSF for mobilizing hematopoietic progenitor cells (HPC) in AL amyloidosis. Bone marrow transplantation 50(4): 610-2	Not pre-emptive or rescue treatment
Dhakal, Binod, Strouse, Christopher, D'Souza, Anita et al. (2014) Plerixafor and abbreviated-course granulocyte colony-stimulating factor for mobilizing hematopoietic progenitor cells in light chain amyloidosis. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 20(12): 1926-31	Not pre-emptive or rescue treatment
Dunn, D., Vikas, P., Jagasia, M. et al. (2012) Plerixafor in AL amyloidosis: improved graft composition and faster lymphocyte recovery after auto-SCT in patient with end-stage renal-disease. Bone marrow transplantation 47(8): 1136-7	Not a relevant study design
Dvorak, Christopher C., Horn, Biljana N., Puck, Jennifer M. et al. (2014) A trial of plerixafor adjunctive therapy in allogeneic hematopoietic cell transplantation with minimal conditioning for severe combined immunodeficiency. Pediatric transplantation 18(6): 602-8	Does not contain a population of people undergoing autologous HSCT treated with plerixafor
Emir, Suna, Demir, Haci Ahmet, Aksu, Tekin et al. (2014) Use of plerixafor for peripheral blood stem cell mobilization failure in children. Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis 50(2): 214-8	Study includes children with solid tumours
Esrick, E. B., Manis, J. P., Daley, H. et al. (2018) Successful hematopoietic stem cell mobilization and apheresis collection using plerixafor alone in sickle cell patients. Blood Advances 2(19): 2505-2512	Does not contain a population of people undergoing autologous HSCT treated with plerixafor

Study	Reason for exclusion
Fadini, Gian Paolo, Fiala, Mark, Cappellari, Roberta et al. (2015) Diabetes Limits Stem Cell Mobilization Following G-CSF but Not Plerixafor. Diabetes 64(8): 2969-77	Study includes population with MM and/or lymphoma
Fowler, C. J., Dunn, A., Hayes-Lattin, B. et al. (2009) Rescue from failed growth factor and/or chemotherapy HSC mobilization with G-CSF and plerixafor (AMD3100): an institutional experience. Bone marrow transplantation 43(12): 909-17	Study includes population with MM and/or lymphoma
Galli, Monica, Lessi, Federica, Rambaldi, Alessandro et al. (2015) Mobilization of peripheral blood hematopoietic stem cells by granulocyte-colony stimulating factor and plerixafor in patients with cardiac AL amyloidosis. Amyloid : the international journal of experimental and clinical investigation : the official journal of the International Society of Amyloidosis 22(4): 259-60	Not pre-emptive or rescue treatment
Garcia-Escobar, I., Parrilla, L., Ortega, L. M. et al. (2014) Clinical experience with plerixafor as a mobilization regimen for autologous peripheral blood stem cell transplantation in patients with refractory germ cell tumors. Molecular and Clinical Oncology 2(6): 923-926	Not a relevant study design
Ghobadi, Armin, Fiala, Mark A., Ramsingh, Giridharan et al. (2017) Fresh or Cryopreserved CD34+-Selected Mobilized Peripheral Blood Stem and Progenitor Cells for the Treatment of Poor Graft Function after Allogeneic Hematopoietic Cell Transplantation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 23(7): 1072-1077	Does not contain a population of people undergoing autologous HSCT treated with plerixafor
Green, Michael M. B., Chao, Nelson, Chhabra, Saurabh et al. (2016) Plerixafor (a CXCR4 antagonist) following myeloablative allogeneic hematopoietic stem cell transplantation enhances hematopoietic recovery. Journal of hematology & oncology 9(1): 71	Does not contain a population of people undergoing autologous HSCT treated with plerixafor
Gregory, Kelly M.; Rao, Kamakshi V.; Armistead, Paul M. (2010) Plerixafor dosing and administration in a patient with dialysis-dependent renal failure. The Annals of pharmacotherapy 44(12): 2028-30	Not a relevant study design
Greil, Christine, Kiote-Schmidt, Chrissoula, Fink, Geertje et al. (2017) Successful peripheral blood stem cell mobilization with a cost-efficient single fixed-dose plerixafor schedule in poor mobilizers. Leukemia & lymphoma 58(8): 1849-1858	Study combines various populations

Study	Reason for exclusion
Hamid, A. A., Markt, S. C., Vicier, C. et al. (2019) Autologous Stem-Cell Transplantation Outcomes for Relapsed Metastatic Germ-Cell Tumors in the Modern Era. Clinical Genitourinary Cancer 17(1): 58	Not a relevant study design
He, Shun, Chu, Jianhong, Vasu, Sumithira et al. (2014) FLT3L and plerixafor combination increases hematopoietic stem cell mobilization and leads to improved transplantation outcome. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 20(3): 309-13	Not a relevant study design
Hong, Kyung Taek, Kang, Hyoung Jin, Kim, Nam Hee et al. (2012) Successful mobilization using a combination of plerixafor and G-CSF in pediatric patients who failed previous chemomobilization with G-CSF alone and possible complications of the treatment. Journal of hematology & oncology 5: 14	Study includes children with solid tumours
Horwitz, M. E., Chute, J. P., Gasparetto, C. et al. (2012) Preemptive dosing of plerixafor given to poor stem cell mobilizers on day 5 of G-CSF administration. Bone marrow transplantation 47(8): 1051-5	Study includes population with MM and/or lymphoma
Hsieh, Matthew M. and Tisdale, John F. (2018) Hematopoietic stem cell mobilization with plerixafor in sickle cell disease. Haematologica 103(5): 749-750	Not a relevant study design
Hubel, K., Fresen, M. M., Salwender, H. et al. (2011) Plerixafor with and without chemotherapy in poor mobilizers: results from the German compassionate use program. Bone marrow transplantation 46(8): 1045-52	Study includes population with MM and/or lymphoma
Jaiswal, Sarita Rani, Bhakuni, Prakash, Joy, Aby et al. (2018) Impact of Single-Dose Plerixafor as an Adjunct to Granulocyte Colony-Stimulating Factor-Based Peripheral Blood Stem Cell Mobilization on the Graft Composition and Outcome for T Cell-Replete Haploidentical Peripheral Blood Stem Cell Transplantation with Post-Transplantation Cyclophosphamide: A Comparative Study. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 24(3): 542-548	Not a relevant study design
Jantunen, E. and Fruehauf, S. (2011) Importance of blood graft characteristics in auto-SCT: implications for optimizing mobilization regimens. Bone marrow transplantation 46(5): 627-35	Study includes population with MM and/or lymphoma

Study	Reason for exclusion
Kamdar, M., Abebe, S., Gonzalez Fontal, G. R. et al. (2017) Administration of plerixafor for peripheral blood CD34+ stem cell content of less than 30 x 10-6/L for autologous stem cell mobilization leads to decreased apheresis days and increased total yield. Bone marrow transplantation. Conference: 43rd annual meeting of the european society for blood and marrow transplantation. France 52(supplement1): 39	Conference abstract
Karponi, Garyfalia, Psatha, Nikoletta, Lederer, Carsten Werner et al. (2015) Plerixafor+G-CSF-mobilized CD34+ cells represent an optimal graft source for thalassemia gene therapy. Blood 126(5): 616-9	Does not contain a population of people undergoing autologous HSCT treated with plerixafor
Kaul, E., Shah, G., Chaulagain, C. et al. (2014) Plerixafor and G-CSF for autologous stem cell mobilization in AL amyloidosis. Bone marrow transplantation 49(9): 1233	Not pre-emptive or rescue treatment
Kobold, S., Isernhagen, J., Hubel, K. et al. (2011) Plerixafor is effective and safe for stem cell mobilization in heavily pretreated germ cell tumor patients. Bone marrow transplantation 46(8): 1053-6	Not a relevant study design
Kosmas, Christos, Athanasopoulos, Aggelos, Dimitriadis, George et al. (2014) Plerixafor added to G-CSF-supported paclitaxel-ifosfamide-cisplatin salvage chemotherapy enhances mobilization of adequate numbers of hematopoietic stem cells for subsequent autografting in hard-to-mobilize patients with relapsed/refractory germ-cell tumors: a single-center experience. Anti-cancer drugs 25(7): 841-7	Not a relevant study design
Lagresle-Peyrou, C., Lefrere, F., Magrin, E. et al. (2018) Plerixafor enables safe, rapid, efficient mobilization of hematopoietic stem cells in sickle cell disease patients after exchange transfusion. Haematologica 103(5): 778-786	Does not contain a population of people undergoing autologous HSCT treated with plerixafor
Leotta, S., Poidomani, M., Mauro, E. et al. (2011) AMD3100 for urgent PBSC mobilization and allogeneic transplantation from a normal donor after failed marrow harvest. Bone marrow transplantation 46(2): 314-6	Not a relevant study design
Lessi, Federica, Marson, Piero, Colpo, Anna et al. (2016) Spontaneous splenic rupture following stem cell mobilization with G-CSF and plerixafor in AL amyloidosis. Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis 54(2): 256-8	Not a relevant study design

Study	Reason for exclusion
Lidonnici, Maria Rosa, Aprile, Annamaria, Frittoli, Marta Claudia et al. (2017) Plerixafor and G-CSF combination mobilizes hematopoietic stem and progenitors cells with a distinct transcriptional profile and a reduced in vivo homing capacity compared to plerixafor alone. Haematologica 102(4): e120-e124	Not a relevant study design
Liesveld, J. (2015) Plerixafor: Potential role in acute leukemia therapy. Expert Opinion on Orphan Drugs 3(4): 467-475	Review article but not a systematic review
Liu, T., Li, X., You, S. et al. (2016) Effectiveness of AMD3100 in treatment of leukemia and solid tumors: From original discovery to use in current clinical practice. Experimental Hematology and Oncology 5(1): 19	Review article but not a systematic review
Lopez-Castano, F., Manresa, P., Diaz, V. et al. (2019) Comparison and cost analysis of three protocols for mobilization and apheresis of haematopoietic progenitor cells. Journal of Clinical Apheresis	Study includes population with MM and/or lymphoma
Maschan, A. A., Balashov, D. N., Kurnikova, E. E. et al. (2015) Efficacy of plerixafor in children with malignant tumors failing to mobilize a sufficient number of hematopoietic progenitors with G-CSF. Bone marrow transplantation 50(8): 1089-91	Study includes children with solid tumours
Mehdizadeh, M., Hajifathali, A., Tabarraee, M. et al. (2013) Plerixafor in the treatment of stem cell mobilization failure; first experience in Iran. Iranian Journal of Pharmaceutical Research 12(suppl): 185-187	Study includes population with MM and/or lymphoma
Micallef, I. N., Jacobsen, E. D., Shaughnessy, P. et al. (2013) G-CSF plus plerixafor (Mozobil) to mobilize hematopoietic stem cells in patients with thrombocytopenia or leukopenia prior to auto-SCT. Bone marrow transplantation 48(2): 303-4	Study includes population with MM and/or lymphoma
Milone, Giuseppe and Tripepi, Giovanni (2014) Algorithms for early identification of poor mobilization and for on-demand use of plerixafor in patients mobilized by chemotherapy and granulocyte-colony stimulating factor. Leukemia & lymphoma 55(3): 725-6	Not a relevant study design
Miltiadous, Constantinos, Dimitriadis, Georgios K., Roditis, Pavlos et al. (2017) Plerixafor mobilization of peripheral blood hematopoietic progenitors to support further high-dose chemotherapy cycles in a patient with germ-cell tumor relapsing after previous tandem high-dose chemotherapy and hematopoietic cell transplantation: report of a case. Anti-cancer drugs 28(2): 237-241	Not a relevant study design

Study	Reason for exclusion
Modak, Shakeel, Cheung, Irene Y., Kushner, Brian H. et al. (2012) Plerixafor plus granulocyte-colony stimulating factor for autologous hematopoietic stem cell mobilization in patients with metastatic neuroblastoma. Pediatric blood & cancer 58(3): 469-71	Study includes children with solid tumours
Mohty, M., Drillat, P., Grouin, J. M. et al. (2017) Addition of plerixafor to G-CSF is useful to achieve efficient collection even in very poor mobilizers: hope for patients with diminished hematopoietic function. Bone marrow transplantation 52(7): 1049-1050	Not a relevant study design
Naithani, Rahul, Sachdeva, Mansi, Rai, Reeta et al. (2016) Plerixafor for Hematopoietic Stem Cell Mobilization in Children With Neuroblastoma. Experimental and clinical transplantation : official journal of the Middle East Society for Organ Transplantation 14(3): 358-9	Study includes children with solid tumours
O'Hara, V. J. D., Karr, A. H., Srivastava, S. et al. (2014) Experience with plerixafor for hematopoietic cell mobilization in nine patients with germ cell tumors. Pharmacotherapy 34(1): 85-88	Not pre-emptive or rescue treatment
Saure, Christian, Weigelt, Christian, Schroeder, Thomas et al. (2010) Plerixafor enables successful hematopoietic stem cell collection in an extensively pretreated patient with testicular cancer. Acta haematologica 124(4): 235-8	Not a relevant study design
Schroeder, Mark A., Rettig, Michael P., Lopez, Sandra et al. (2017) Mobilization of allogeneic peripheral blood stem cell donors with intravenous plerixafor mobilizes a unique graft. Blood 129(19): 2680-2692	Does not contain a population of people undergoing autologous HSCT treated with plerixafor
Selleslag, D., Dierickx, D., Breems, D. A. et al. (2011) Plerixafor in poor stem cell mobilizers: the Belgian Compassionate Use Program. Acta clinica Belgica 66(3): 200-4	Study includes population with MM and/or lymphoma
Sevilla, Julian, Schiavello, Elisabetta, Madero, Luis et al. (2012) Priming of hematopoietic progenitor cells by plerixafor and filgrastim in children with previous failure of mobilization with chemotherapy and/or cytokine treatment. Journal of pediatric hematology/oncology 34(2): 146-50	Study includes children with solid tumours

Study	Reason for exclusion
Sheppard, Dawn, Bredeson, Christopher, Allan, David et al. (2012) Systematic review of randomized controlled trials of hematopoietic stem cell mobilization strategies for autologous transplantation for hematologic malignancies. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 18(8): 1191-203	Study includes population with MM and/or lymphoma
Shimizu, N., Sakaida, E., Ohwada, C. et al. (2012) Mobilization of PBSCs in poor mobilizers with POEMS syndrome using G-CSF with plerixafor. Bone marrow transplantation 47(12): 1587-8	Not a relevant study design
Son, Meong Hi, Kang, Eun Suk, Kim, Dong Hwan et al. (2013) Efficacy and toxicity of plerixafor for peripheral blood stem cell mobilization in children with high-risk neuroblastoma. Pediatric blood & cancer 60(8): E57-9	Study includes children with solid tumours
Spoerl, Silvia, Peter, Robert, Wascher, Dagmar et al. (2017) Patients' outcome after rescue plerixafor administration for autologous stem cell mobilization: a single-center retrospective analysis. Transfusion 57(1): 115-121	Study includes population with MM and/or lymphoma
Srinivasan, Ashok, Panetta, John C., Cross, Shane J. et al. (2014) Phase I study of the safety and pharmacokinetics of plerixafor in children undergoing a second allogeneic hematopoietic stem cell transplantation for relapsed or refractory leukemia. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 20(8): 1224-8	Does not contain a population of people undergoing autologous HSCT treated with plerixafor
Tanhehco, Yvette C., Adamski, Jill, Sell, Mary et al. (2010) Plerixafor mobilization leads to a lower ratio of CD34+ cells to total nucleated cells which results in greater storage costs. Journal of clinical apheresis 25(4): 202-8	Study includes population with MM and/or lymphoma
Teusink, Ashley, Pinkard, Susan, Davies, Stella et al. (2016) Plerixafor is safe and efficacious for mobilization of peripheral blood stem cells in pediatric patients. Transfusion 56(6): 1402-5	Study includes children with solid tumours
Toledano, Helen, Yahel, Anat, Cohen, Ian J. et al. (2010) Successful mobilization, harvest and transplant of peripheral blood stem cells using AMD3100 and G-CSF following high dose craniospinal irradiation for medulloblastoma in a young child. Pediatric blood & cancer 54(4): 613-5	Study includes children with solid tumours

Study	Reason for exclusion
Tuffaha, Haitham and Abdel-Rahman, Fawzi Abdel-Latif (2010) Successful stem-cell mobilization and transplantation using plerixafor in a patient with a germ cell tumor. Hematology/oncology and stem cell therapy 3(4): 203-5	Not a relevant study design
Veeraputhiran, Muthu, Jain, Tania, Cronin, Simon et al. (2014) Successful hematopoietic stem cell collection in patients who fail initial plerixafor mobilization for autologous stem cell transplant. Journal of clinical apheresis 29(6): 293-8	Study includes population with MM and/or lymphoma
Vettenranta, Kim; Mottonen, Merja; Riikonen, Pekka (2012) The use of plerixafor in harvesting autologous stem cells in the pediatric setting. Pediatric blood & cancer 59(1): 197-8	Study includes children with solid tumours
Vishnu, Prakash, Roy, Vivek, Paulsen, Athena et al. (2012) Efficacy and cost-benefit analysis of risk-adaptive use of plerixafor for autologous hematopoietic progenitor cell mobilization. Transfusion 52(1): 55-62	Study includes population with MM and/or lymphoma
Vives, S., Sancho, J. M., Almazan, F. et al. (2012) Plerixafor plus G-CSF in combination with chemotherapy for stem cell mobilization in a pediatric patient with Ewing's sarcoma. Journal of Clinical Apheresis 27(5): 260-262	Study includes children with solid tumours
Worel, Nina, Fritsch, Gerhard, Agis, Hermine et al. (2017) Plerixafor as preemptive strategy results in high success rates in autologous stem cell mobilization failure. Journal of clinical apheresis 32(4): 224-234	Study includes population with MM and/or lymphoma
Yannaki, E., Papayannopoulou, T., Jonlin, E. et al. (2012) Erratum: "hematopoietic stem cell mobilization for gene therapy of adult patients with severe beta-Thalassemia: Results of clinical trials using G-CSF or plerixafor in splenectomized and nonsplenectomized subjects" (Molecular Therapy (2012) 20 (230-238) DOI: 10.1038/mt.2011.195). Molecular Therapy 20(2): 469	Does not contain a population of people undergoing autologous HSCT treated with plerixafor
Yannaki, E., Papayannopoulou, T., Jonlin, E. et al. (2011) Hematopoietic Stem Cell Mobilization for Gene Therapy of Adult Patients With Severe beta-Thalassemia: Results of Clinical Trials Using G-CSF or plerixafor in Splenectomized and Nonsplenectomized Subjects. Molecular Therapy	Does not contain a population of people undergoing autologous HSCT treated with plerixafor

Study	Reason for exclusion
Yannaki, Evangelia, Karponi, Garyfalia, Zervou, Fani et al. (2013) Hematopoietic stem cell mobilization for gene therapy: superior mobilization by the combination of granulocyte-colony stimulating factor plus plerixafor in patients with beta-thalassemia major. Human gene therapy 24(10): 852-60	Does not contain a population of people undergoing autologous HSCT treated with plerixafor
Yannaki, Evangelia, Papayannopoulou, Thalia, Jonlin, Erica et al. (2012) Hematopoietic stem cell mobilization for gene therapy of adult patients with severe beta-thalassemia: results of clinical trials using G-CSF or plerixafor in splenectomized and nonsplenectomized subjects. Molecular therapy : the journal of the American Society of Gene Therapy 20(1): 230-8	Does not contain a population of people undergoing autologous HSCT treated with plerixafor
Yuan, Shan, Wang, Shirong, Salhotra, Amandeep et al. (2014) Plerixafor to the rescue: boosting peripheral blood stem cell mobilization in patients previously treated with hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate, cytarabine (Hyper-CVAD) chemotherapy. Leukemia & lymphoma 55(7): 1557-62	Study includes population with MM and/or lymphoma

References for the three most clinically impactful studies were submitted with the Preliminary Policy Proposition. These are listed in the following table with the evidence selection decision and rationale for each provided:

Study	Comment
Worel N, Apperley J, Basak G, Douglas K, Gabriel I, et al. (2012). European data on stem cell mobilization with plerixafor in patients with nonhematologic disease: an analysis of the European consortium of stem cell mobilization. Transfusion 52, pp 2395- 2400	Included in the evidence summary on non-haematologic tumours
Horwitz M, Long, Holman P, Libby E, Calandra G, Schriber J. (2012). Efficacy and safety of hematopoietic stem cell remobilization with plerixafor +G-CSF in adult patients with germ cell tumours. Bone Marrow Transplantation, 47, 1287-1286.	Included in the evidence summary on non-haematologic tumours
Jaimovich G, Castro M, Ostriz B, Fernandez M, Silveyra D, Campestri R. (2016). Plerixafor, cyclophosphamide and G-CSF and blood cell mobilization in a patient with acute promyelocytic leukaemia. Journal of Clinical Apheresis, 32, pp 592-593.	Excluded: not a relevant study design

12. Related NICE guidance and NHS England clinical policies

NHS England has published clinical commissioning policies on haematopoietic stem cell transplantation and plerixafor for stem cell mobilisation. NICE has not issued any guidance on plerixafor for stem cell mobilisation.

13. Terms used in this evidence summary

Abbreviations

Term	Definition
AL amyloidosis	Amyloid light-chain amyloidosis
G-CSF	Granulocyte-colony stimulating factor
HSCT	Haematopoietic stem cell transplantation
PBSC	Peripheral blood stem cells

Medical definitions

Term	Definition
Allogeneic stem cell transplant	A procedure in which a person receives haematopoietic stem cells (cells from which all blood cells develop) from a genetically similar donor
Apheresis	The name given to the flow of the person's blood through the cell separator during which the stem cells (PBSC) are separated and collected into a separate container in which they can then be frozen for later use
Autologous stem cell transplant	The process of high-dose chemotherapy followed by infusion of the harvested stem cells which will repopulate the bone marrow and allow the recovery of the person's blood counts
CD34+ cell	The protein expressed on the stem cells (PBSC) that can be detected, allowing the number of stem cells in the blood or the harvest to be counted
Haematological	Relating to the blood and blood forming tissues
Haematopoietic stem cells	Cells in the bone marrow that can develop into different types of blood cells
Haematopoietic stem cell transplantation	Blood and bone marrow transplantation
Lymphoma	A cancer that affects cells of the immune system called 'lymphocytes'
Myeloma	A cancer that affects the bone marrow
Neutrophil	The most common type of white blood cell
Peripheral blood stem cells	Stem cells in the circulating blood flow, rather than in the bone marrow
Platelet	A type of blood cell that helps blood clot
Pre-emptive treatment	Use of plerixafor when there is a low level of circulating PBSC on the day of planned collection
Rescue treatment	Use of plerixafor with high-dose G-CSF when a previous attempt at mobilisation has failed to collect enough PBSC
Solid tumours	Solid tumours may be benign (not cancer), or malignant (cancer). Different types of solid tumours are named for the type of cells that form them. Examples of solid tumours are sarcomas, carcinomas, and lymphomas. Leukaemias (cancers of the bone marrow and blood) generally do not form solid tumours
Stem cell harvest	Collection of the stem cells (PBSC) from the blood using a cell separator machine
Stem cell mobilisation	A process to dislodge the stem cells from the bone marrow and increase the amount circulating in the blood from where they can be collected

14. References

Lee SY, Sanchorawala V, Seldin DC et al. (2014) Plerixafor-augmented peripheral blood stem cell mobilization in AL amyloidosis with cardiac involvement: a case series. Amyloid (3): 149–53

Mozobil European public assessment report

Mozobil summary of product characteristics

NHS England Clinical Commissioning Policy Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised January 2015

NHS England Clinical Commissioning Policy Use of Plerixafor for Stem Cell Mobilisation (updated to include paediatrics) August 2016