PUBLIC SUMMARY DOCUMENT

Product: Plerixafor 24 mg/1.2 mL, injection, subcutaneous infusion, 1.2 mL vial Mozobil®

Sponsor: Sanofi-Aventis Australia Pty Ltd

Date of PBAC Consideration: November 2013

1. Purpose of Application

The re-submission sought a Section 100 (Highly Specialised Drugs Program) Authority Required (+/- STREAMLINED) listing for use in combination with granulocyte-colony stimulating factor (G-CSF), in patients with multiple myeloma or lymphoma requiring an autologous stem cell transplant (ASCT) who meet certain criteria.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This was the fourth consideration by the PBAC of a submission requesting Section 100 (Highly Specialised Drugs Program) listing of plerixafor.

The PBAC previously rejected submissions for plerixafor at its meetings in November 2010, November 2011 and July 2012. Public Summary Documents are available on the PBS website.

The key differences between the July 2012 re-submission and the November 2013 re-submission are presented in the table below.

Key differences between between the July 2012 and the current submission for plerixafor

	Submission considered in July 2012	Current re-submission
Restriction	The definitions of failed mobilisers or rescue of failing mobilisers, e.g. CD34+ thresholds, were not included in restrictions. The Pre-PBAC response proposed definitions.	The proposed listing included definitions for failed mobilisers (yield < 2.0×10^6 CD34+ cells/kg at previous attempt(s)) and rescue of failing mobilisers (peripheral CD34+ cell count ≤ 10 cells/μL or Day 1 yield < 1.0×10^6 CD34+ cells/kg).
Requested price		Reduced compared to the July 2012 re-submission
Comparator	G-CSF in combination with chemotherapy (ifosfamide + carboplatin + etoposide for lymphoma; and cyclophosphamide for multiple myeloma)	Approximately 45% of failed mobilisers with lymphoma will be re-mobilised with cyclophosphamide plus G-CSF after completion of disease-specific chemotherapy.
Clinical evidence	A total of 19 non-randomised studies and observational cohorts.	A total of 59 non-randomised studies and observational cohorts. Of these, 47 studies were new to the re-submission. Data on first-line mobilisation were new to the re-submission.

Economic evaluation	Modelled cost-effectiveness analysis (cost per additional successful mobilisation). The ICERs per additional patient achieving successful mobilisation were: - between $15,000 and $ 45,000 for failed mobilisers with lymphoma; - less than $15, 000 for failed mobilisers with multiple myeloma; - less than $15, 000 for rescue of failing mobilisers with lymphoma; and - less than $15, 000 for rescue of failing mobilisers with multiple myeloma.	Updated with significant changes to inputs. The resultant ICERs per additional patient achieving successful mobilisation were: - between $105,000 and $200,000 for failed mobilisers with lymphoma; - between $15,000 and $ 45,000 for failed mobilisers with multiple myeloma; - between $15,000 and $ 45,000 for rescue of failing mobilisers with lymphoma; and -- less than $15, 000 for rescue of failing mobilisers with multiple myeloma.
Financial estimates	Cost of plerixafor to the PBS (less co-payments): Less than $10 million in Year 5 with a cumulative total of between $10 million and $30 million over the first 5 years of listing	Updated with a different approach. Cost of plerixafor to the PBS (less co-payments): Less than $10 million in Year 1, with a cumulative total of between $10 million and $30 million over the first five years of listing. Cost-offsets with reduced drug and MBS item usage were also claimed.
RSA proposal	Confidential rebate for any sales above thresholds from financial estimates for Year 1 to 5 post-listing.	No details provided.

Abbreviations: G-CSF, granulocyte-colony stimulating factor; ICER, incremental cost-effectiveness ratio; RSA, risk sharing agreement

3. Registration Status

Plerixafor was TGA registered on 31 May 2010 for use, in combination with granulocyte-colony stimulating factor (G-CSF) to mobilise haematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drug Program)
Public Hospital – Authority Required (Streamlined)
Private Hospital – Authority Required
Treatment, in combination with granulocyte-colony stimulating factor (G-CSF) in an adult patient with multiple myeloma or lymphoma who requires autologous stem cell transplantation and who is undergoing a stem cell mobilisation to collect peripheral blood (PB) CD34+ stem cells and who meets the following conditions:

a) Re-mobilisation in a patient following a previous failed mobilisation attempt, AND with failure defined as stem cell yield < 2.0 x 10^6 CD34+ cells /kg at previous mobilisation attempt(s)

OR

b) Rescue of a failing mobilisation in a mobilisation-naïve patient for whom the intent is to proceed to ASCT within 6 months, AND with failing defined as:
i) the PB CD34+ count is ≤ 10 / μL after the WBC count has risen to ≥ 2 x 10^9 / L, or after at least 4 days of G-CSF treatment, OR
ii) First day stem cell harvest < 1.0 x 10^6 CD34+ cells / kg

NOTES:
No more than 2 vials will be authorised per patient
At the time of authorisation the following information must be recorded

- The timing of PB CD34+ collection relative to GCSF administration
- The PB CD34+ count
- The total white blood cell (WBC) count

The requested price per vial was reduced in the re-submission compared to the July 2012 submission.

Listing was requested on the basis of a cost-effectiveness analysis versus current mobilisation regimens.

The PBAC considered there to be a considerable risk of leakage beyond the proposed PBS population into a lower risk population where cost-effectiveness of plerixafor has not been established.

5. Clinical Place for the Proposed Therapy

High dose chemotherapy with autologous stem cell transplantation is a highly effective treatment for patients with haematological malignancies who are fit enough to undergo this form of therapy. Before transplantation can take place, patients must undergo stem cell mobilisation to increase the number of peripheral blood stem cells available for collection and subsequent autologous transplantation. Currently, most patients are mobilised with G-CSF alone, or G-CSF with chemotherapy.

Despite developments in peripheral blood stem cells mobilisation and collection techniques, a proportion of patients can undergo repeated mobilisation attempts and still fail to collect enough cells for stem cell transplantation. These patients are commonly referred to as "failed mobilisers". Although mobilisation protocols can vary between institutions, failed mobilisers are usually defined as those patients who fail to collect the minimum CD34+ cell yield for transplant (2 x 10^6 CD34+ cells/kg) (Mohty et al., 2011) or those patients who are unable to proceed to apheresis because of low peripheral blood CD34+ cell counts. The respondents to the Sponsor's Australian Treatment Practice Survey provided thresholds of peripheral blood CD 34+ cell counts ranging from 5 to 20 cells/μL to proceed to apheresis.[!] In general, patients who fail mobilisation tend to be older, more heavily pre-treated and have more extensive disease (Sugrue *et al.*, 2000). The delay in treatment that results from a failure to mobilise further increases the chances of disease progression.

As in the July 2012 re-submission, the current re-submission proposed that the place in therapy of plerixafor, in combination with[£] G-CSF, is for the treatment of patients who are

failed mobilisers or those who are failing mobilisation (immediate savage) and who will subsequently undergo ASCT for lymphoma and multiple myeloma patients.

6. Comparator

As in July 2012, the re-submission nominated G-CSF in combination with chemotherapy (ifosfamide + carboplatin + etoposide for lymphoma; and cyclophosphamide for multiple myeloma) as the comparator.

The PBAC noted that the nature of the comparator chemotherapy agent for lymphoma patients had changed since the July 2012 re-submission. The current re-submission claimed that approximately 45% of failed mobilisers with lymphoma will be re-mobilised with additional cyclophosphamide plus G-CSF after the completion of disease specific chemotherapy (such as ifosfamide + carboplatin + etoposide). The PBAC noted that this change was applied to the economic model and financial estimates to claim cost-offsets associated with chemotherapy-based mobilisation (chemo-mobilisation) for lymphoma patients. The PBAC considered that this change was reasonable (i.e., "off the back" of disease-specific regimens or cyclophosphamide + G-CSF after the completion of disease-specific salvage chemotherapy).

7. Clinical Trials

No head-to-head randomised trials were presented in the re-submission. The re-submission was based on 59 non-randomised studies, 47 of which had not previously been considered by the PBAC. Three studies from the July 2012 re-submission have updated data and one study has been reclassified from the rescue of failing mobilisers population to the failed mobilisers population. The evidence presented in the current and July 2012 re-submissions are summarised in the following table.

Evidence included in the current and July 2012 re-submissions

	July 2012	Current re-submission
Number of publications	19 studies	59 studies
Failed mobilisers (plerixafor)	13 studies/13 datasets/1,071 pts (overlap of up to 250 pts)	19 studies/19 datasets/1,053 pts
Failed mobilisers (comparator)	4 studies/4 datasets/109 pts	9 studies/9 datasets/741 pts
Rescue of failing mobilisers	6 studies/6 datasets/129 pts	18 studies/24 datasets/801 pts
First-line mobilisation with plerixafor	-	10 studies/10 datasets/450 pts
First-line mobilisation with comparator	-	23 studies/27 datasets/4,169 pts

Abbreviations: pts, patients

The table below details the list of studies presented in the re-submission.

Non-randomised studies included in the re-submission

Study ID	Protocol title/ Publication title	Publication citation
Failed mobilisers (plerixafor); Failed mobilisers (chemotherapy); First-line mobilisation (chemotherapy)		
Pusic (2008)[a]	Pusic I, Jiang SY, Landua S, Uy GL, Rettig MP, *et al*. Impact of mobilization strategies on achieving sufficient stem cell yields for	*Biology of Blood and Marrow Transplantation* 2008; 14: 1045-1056.

Study ID	Protocol title/ Publication title	Publication citation
	autologous transplantation.	
Failed mobilisers (plerixafor); Failed mobilisers (chemotherapy)		
Perkins (2012)	Perkins JB, Shapiro JF, Bookout RN, Yee GC, Anasetti CA, *et al.* Retrospective comparison of filgrastim plus plerixafor to other regimens for remobilization after primary mobilization failure: Clinical and economic outcomes.	*American Journal of Haematology* 2012; 87: 673-677.
Abdel-Rahman (2013)	Abdel-Rahman F, Tuffaha HW, Sharma S, Jazar HA, Hussein N, *et al.* GCSF with or without chemotherapy compared to Plerixafor with GCSF as salvage mobilization regimen in patients with multiple myeloma and lymphoma: Collection effectiveness and cost effectiveness analysis.	*Journal of Oncology Pharmacy Practice* 2013 [*Epub ahead of print*]
Failed mobilisers (plerixafor); Rescue of failing mobilisers (plerixafor); First-line mobilisation (plerixafor)		
Cooper (2011)[a]	Cooper DL, Pratt K, Baker J, Medoff E, Conkling-Walsh A, *et al.* Late afternoon dosing of plerixafor for stem cell mobilization: A practical solution.	*Clinical Lymphoma, Myeloma & Leukaemia* 2011; 11(3): 267-72.
Failed mobilisers (plerixafor); First-line mobilisation (plerixafor); First-line mobilisation (chemotherapy)		
Campen (2011) (abstract)	Campen, CJ, Yeager AM, Green MR, Armstrong EP. Comparative cost-effectiveness of plerixafor plus granulocyte-colony stimulating factor versus cyclophosphamide plus granulocyte-colony stimulating factor for autologous peripheral blood stem cell mobilization in patients with multiple myeloma.	*Biology of Blood and Marrow Transplantation* 2011; 17(2): S349.
Failed mobilisers (plerixafor); Rescue of failing mobilisers (plerixafor)		
Tricot (2010)	Tricot G, Cottler-Fox MH, Calandra G. Safety and efficacy assessment of plerixafor in patients with multiple myeloma proven or predicted to be poor mobilizers, including assessment of tumor cell mobilization.	*Bone Marrow Transplantation* 2010; 45: 63–68.
Abhyankar (*2012*)	Abhyankar S, DeJarnette S, Aljitawi O, Ganguly S, Merkel D, *et al.* A risk-based approach to optimize autologous hematopoietic stem cell (HSC) collection with the use of plerixafor.	*Bone Marrow Transplantation 2012; 47(4): 483-7*
Albo Lopez (2013) EHA poster	Albo López C, Gonzàlez Rodríguez R, Gonzàlez Pérez S, Labilla Rubira E, Dios Loureiro A, *et al.* Two different plerixafor stem cell mobilization strategies. A multicentre experience.	Poster presented at EHA 2013.
Failed mobilisers (plerixafor); First-line mobilisation (plerixafor)		
Basak (2011c)	*Basak GW, Jaksic O, Koristek Z, Mikala G, Basic-Kinda S, et al. Haematopoietic stem cell mobilization with plerixafor and G-CSF in patients with multiple myeloma transplanted with autologous stem cells.*	*European Journal of Haematology 2011; 86(6): 488-95.*
Lor (2012)	Lor KW, Helmons PJ, Belew H, Lane JR, Ball ED. Plerixafor as first- and second-line strategies for autologous stem cell mobilization in patients with non-Hodgkin's lymphoma or multiple myeloma.	*Pharmacotherapy* 2012; 32(7): 596 –603.
Failed mobilisers (chemotherapy); First-line mobilisation (chemotherapy)		
Wuchter	Wuchter P, Ran D, Bruckner T, Schmitt T,	*Biology of Blood and*

Study ID	Protocol title/ Publication title	Publication citation
(2010)	Witzens-Harig M, *et al.* Poor mobilization of hematopoietic stem cell- definitions, incidence, risk factors, and impact on outcome of autologous transplantation.	*Marrow Transplantation* 2010; 16: 490-499.
Sancho (2012)	Sancho JM, Morgades M, Grifols J-R, Juncà J, Guardia R, *et al.* Predictive factors for poor peripheral blood stem cell mobilization and peak CD34+ cell count to guide pre-emptive or immediate rescue mobilization.	*Cytotherapy* 2012; 14: 823-829.
Failed mobilisers (chemotherapy); *First-line mobilisation (G-CSF alone)*		
Gertz (2010)	Gertz MA, Wolf RC, Micallef INM, Gastineau DA. Clinical impact and resource utilization after stem cell mobilization failure in patients with multiple myeloma and lymphoma.	*Bone Marrow Transplantation* 2010; 45: 1396-1403.
Rescue of failing mobilisers (plerixafor); First-line mobilisation (chemotherapy)		
Li (2011)[a]	Li J, Hamilton E, Vaughn L, Graiser M, Renfroe H, *et al.* Effectiveness and cost analysis of "just-in-time" salvage plerixafor administration in autologous transplant patients with poor stem cell mobilization kinetics.	*Transfusion* 2011; 51: 2175-2182.
Micallef (2013)	Micallef INM, Sinha S, Gastineau DA, Wolf R, Inwards DJ, *et al.* Cost-effectiveness analysis of a risk-adapted algorithm of plerixafor use for autologous peripheral blood stem cell mobilization.	*Biology of Blood and Marrow Transplantation* 2013; 19: 87-93.
Milone (2013a) EHA poster	*Milone G, Scalzulli P, Martino M, Sortino G et al. Plerixafor on demand.*	*Poster presented at EHA 2013.*
***First-line mobilisation (plerixafor);* First-line mobilisation (chemotherapy)**		
Awan (2013)	Awan F, Kochuparambil ST, Falconer DE, Cumpston A, Leadmon S, *et al.* Comparable efficacy and lower cost of PBSC mobilization with intermediate-dose cyclophosphamide and G-CSF compared with plerixafor and G-CSF in patients with multiple myeloma treated with novel therapies.	*Bone Marrow Transplantation* 2013: 1–6. [*Epub ahead of print*]
Chaudhary (2013)	Chaudhary L, Awan F, Cumpston A, Leadmon S, Watkins K, *et al*. Peripheral blood stem cell mobilization in multiple myeloma patients treat in the novel therapy-era with plerixafor and G-CSF has superior efficacy but significantly higher costs compared to mobilization with low-dose cyclophosphamide and G-CSF.	*Journal of Clinical Apheresis* 2013. [*Epub ahead of print*]
First-line mobilisation (plerixafor); First-line mobilisation (G-CSF alone)		
Cashen (2008)	Cashen A, Lopez S, Gao F, Calandra G, MacFarland R, *et al.* A phase II study of plerixafor (AMD3100) plus G-CSF for autologous hematopoietic progenitor cell mobilization in patients with Hodgkin lymphoma.	*Biology of Blood and Marrow Transplantation* 2008; 14; 1253-1261.
First-line mobilisation (chemotherapy); First-line mobilisation (G-CSF alone)		
Duong (2011)	Duong HK, Bolwell BJ, Rybicki L, Koo A, Hsi ED, *et al.* Predicting hematopoietic stem cell mobilization failure in patients with multiple myeloma: A simple method using day 1 CD34+ cell yield.	*Journal of Clinical Apheresis* 2011; 26:111–115.
Failed mobilisers (plerixafor)		
Calandra (2008)	Calandra G, McCarty J, McGuirk J, Tricot G, Crocker SA, *et al*. AMD3100 plus G-CSF can	*Bone Marrow Transplantation* 2008;

Study ID	Protocol title/ Publication title	Publication citation
	successfully mobilize CD34+ cells from non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma patients previously failing mobilization with chemotherapy and/or cytokine treatment: Compassionate use data.	41(4): 331–338.
Fowler (2009)	Fowler CJ, Dunn A, Hayes-Lattin B, Hansen K, Hansen L, *et al*. Rescue from failed growth factor and/ or chemotherapy HSC mobilization with G-SCF and plerixafor (AMD3100): an institutional experience.	*Bone Marrow Transplantation* 2009; 43: 909-917.
Hubel (2012) (previously cited as 2011a, Article-In-Press)	Hübel K, Fresen MM, Apperley JF, Basak GW, Douglas KW, *et al.* European data on stem cell mobilization with plerixafor in non-Hodgkin's lymphoma, Hodgkin's lymphoma and multiple myeloma patients. A subgroup analysis of the European Consortium of stem cell mobilization.	*Bone Marrow Transplantation* 2012; 47: 1046 -1050.
Andreola (2011a) (*abstract*)	Andreola G, Laszlo D, Sammassimo S, Babic A, Rabascio C, *et al. Plerixafor as mobilizing agent for patients failing a previous mobilization attempt and as first-line mobilizing therapy in patients affected by multiple myeloma.*	*Bone Marrow Transplantation 2011 (abstract)*
Basak (2011b)[b]	Basak GW, Mikala G, Koristenk Z, Jaksic O, Basic-Kinda S, *et al.* Plerixafor to rescue failing chemotherapy-based stem cell mobilization: it's not too late.	*Leukemia & Lymphoma* 2011; 52(9): 1711-1719.
Micallef (2011)	Micallef INM, Ho AD, Klein LM, Marulkar S, Gandhi PJ, *et al.* Plerixafor (Mozobil) for stem cell mobilization in patients with multiple myeloma previously treated with lenalidomide.	*Bone Marrow Transplantation* 2011; 46: 350–355.
Tekgündüz (2012)	Tekgündüz E, Altuntaş F, Şıvgın S, Akı ŞZ, Dönmez A, et al. Plerixafor use in patients with previous mobilization failure: A multicenter experience.	*Transfusion and Apheresis Science* 2012; 47: 77–80.
Lefrère (2013)	Lefrère F, Mauge L, Réa D, Ribeil J-A, Dal Cortivo L, *et al.* A specific time course for mobilization of peripheral blood CD34+ cells after plerixafor injection in very poor mobilizer patients: impact on the timing of the apheresis procedure.	*Transfusion* 2013; 53(3): 564-569.
Bhutani (2013)	Bhutani D, Zonder J, Valent J, Tageja N, Ayash L, *et al.* Evaluating the effects of lenalidomide induction therapy on peripheral stem cells collection in patients undergoing autologous stem cell transplant for multiple myeloma.	*Support Care Cancer* 2013; DOI 10.1007/s00520-013-1808-5. [*Epub ahead of print*]
Failed mobilisers (chemotherapy)		
Goterris (2005)	Goterris R, Hernández-Boluda JC, Teruel A, Gómez C, Lis MJ, *et al.* Stem Cell Procurement: Impact of different strategies of second- line stem cell harvest on the outcome of autologous transplantation in poor peripheral blood stem cell mobilizers.	*Bone Marrow Transplantation* 2005; 36: 847-853.
McKibbin (2007)	McKibbin T, Burzynski J, Greene R, Ochoa-Bayona J, Tsai TW, *et al.* Paclitaxel and filgrastim for hematopoietic progenitor cell mobilization in patients with hematologic malignancies after failure of a prior mobilization regimen.	*Leukemia & Lymphoma* 2007; 48(12): 2360-2366.

Study ID	Protocol title/ Publication title	Publication citation
Hill (2012) (letter)	Hill QA, Pearce R, Cook G. Unsuccessful stem cell remobilization for autologous transplantation is predicted by renal impairment and a stem cell yield ≤0.5 X 10^6 CD34+ cells/kg at first mobilization.	*Bone Marrow Transplantation* 2012; 47: 1372-1373.
Rescue of failing mobilisers (plerixafor)		
D'Addio (2011)	D'Addio A, Curti A, Worel N, Douglas K, Motta MR, *et al.* The addition of plerixafor is safe and allows adequate PBSC collection in multiple myeloma and lymphoma patient's poor mobilizers after chemotherapy and G-CSF. D'Addio A, Curti A, Worel N, Motta MR, Rizzi S, *et al.* The addition of plerixafor allows adequate PBSC collection in multiple myeloma and lymphoma patients poor-mobilizers after chemotherapy and G-CSF (abstract).	*Bone Marrow Transplantation* 2011; 46:356-363. *Bone Marrow Transplantation* 2010: S320
Basak (2011a)	Basak GW, Knopinska-Posluszny W, Matuszak M, Kisiel E, Hawrylecka D, *et al.* Hematopoietic stem cell mobilization with the reversible CXCR4 receptor inhibitor plerixafor (AMD3100) - Polish compassionate use experience.	*Annals of Haematology* 2011; 90: 557–568.
Gopal (2012)	Gopal AK, Karami M, Mayor J, Macebeo M, Linenberger M, *et al.* The effective use of plerixafor as a real-time rescue strategy for patients poorly mobilizing autologous CD34+ cells.	*Journal of Clinical Apheresis* 2012; 27: 81-87.
Chen (2012)	Chen A, Bains T, Murray S, Knight R, Shoop K, *et al.* Clinical experience with a simple algorithm for plerixafor utilization in autologous stem cell mobilization.	*Bone Marrow Transplantation* 2012; 47: 1526–1529.
Vishnu (2012)	Vishnu P, Roy V, Paulsen A & Zubair AC. Efficacy and cost-benefit analysis of risk-adaptive use of plerixafor for autologous hematopoietic progenitor cell mobilization.	*Transfusion* 2012; 52: 55-62.
Awan (2012)	Awan FT, Kochuparambil ST, DeRemer D, Cumpston A, Craig M, *et al.* Plerixafor salvage is safe and effective in hard-to-mobilize patients undergoing chemotherapy and filgrastim-based peripheral blood progenitor cell mobilization.	*Journal of Oncology* 2012: *doi: 10.1155/2012/931071*
Horwitz (2012)	Horwitz ME, Chute JP, Gasparetto C, Long GD, McDonald C, *et al.* Pre-emptive dosing of plerixafor given to poor stem cell mobilizers on day 5 of G-CSF administration.	*Bone Marrow Transplantation* 2012; 47: 1051–1055.
Varmavuo (2012)	Varmavuo V, Mäntymaa P, Kuittinen T, Nousiainen T, Jantunen E. Pre-emptive plerixafor injection increases blood neutrophil, lymphocyte and monocyte counts in addition to CD34+ counts in patients with non-Hodgkin lymphoma mobilizing poorly with chemotherapy plus G-CSF: Potential implications for apheresis and graft composition.	*Transfusion and Apheresis Science* 2012; 46: 257–262.
Yuan (2013a) (letter)	Yuan S, Nademanee A, Forman SJ, Wang S. Use of plerixafor in patients with Hodgkin lymphoma with poor mobilization of peripheral blood stem cells.	*Leukemia & Lymphoma* 2013; 54(3): 646-648.
Sanchez Anton (2013) EHA poster	Sànchez Anton MP, Antelo ML, Zabalza A, Zalba S, Anzar M, *et al*. Prediction of mobilization failure for pre-emptive plerixafor	Poster presented at EHA 2013.

Study ID	Protocol title/ Publication title	Publication citation
	administration: The pamplona protocol.	
Smith (2013)	Smith VR, Popat U, Ciurea S, Nieto Y, Anderlini P, *et al.* Just-in-time rescue plerixafor in combination with chemotherapy and granulocyte-colony stimulating factor for peripheral blood progenitor cell mobilization.	*American Journal of Hematology* 2013; doi: 10.1002/ajh.23499:1-21. [*Epub ahead of print*]
First-line mobilisation (plerixafor)		
Andreola (2011b)	Andreola G, Babic A, Rabascio C, Negri M, Martinelli G *et al.* Plerixafor and Filgrastim XM02 (Tevagastrim) as a first line peripheral blood stem cell mobilisation strategy in patients with multiple myeloma and lymphoma candidated to autologous bone marrow transplantation.	*European Journal of Haematology* 2011; 88: 154-158.
Russell (2013)	Russell N, Douglas K, Ho AD, Mohty M, Carlson K, *et al.* Plerixafor and granulocyte colony-stimulating factor for first-line steady-state autologous peripheral blood stem cell mobilization in lymphoma and multiple myeloma: results of the prospective PREDICT trial.	*Haematologica* 2013; 98(2): 172-178.
Shaughnessy (*2013*)	Shaughnessy P, Uberti J, Devine S, Maziarz RT, Vose J, *et al.* Plerixafor and G-CSF for autologous stem cell mobilization in patients with NHL, Hodgkin's lymphoma and multiple myeloma: results from the expanded access program.	*Bone Marrow Transplantation* 2013; 48(6):777-81
First-line mobilisation (chemotherapy)		
Lefrere (1999)	Lefrere J, Makke J, Fermand JP, Marolleau JP, Cortivo LD, *et al.* Blood stem cell collection using chemotherapy with or without systematic G-CSF: experience in 52 patients with multiple myeloma.	*Bone Marrow Transplantation* 1999; 24: 463–466.
Watts (2000)	Watts MJ, Ings SJ, Leverett D, MacMillan A, Devereux S, *et al.* ESHAP and G-CSF is a superior blood stem cell mobilizing regimen compared to cyclophosphamide 1.5 g m^-2 and G-CSF for pre-treated lymphoma patients: a matched pairs analysis of 78 patients.	*British Journal of Cancer* 2000; 82(2): 278–282
Pavone (2002)	Pavone V, Gaudio F, Guarini A, Perrone T, Zonno A, *et al.* Mobilization of peripheral blood stem cells with high-dose cyclophosphamide or the DHAP regimen plus G-CSF in non-Hodgkin's lymphoma.	*Bone Marrow Transplantation* 2002; 29: 285–290.
Hill (2007)	Hill QA, Buxton D, Pearce R, Gesinde MO, Smith GM *et al.* An analysis of the optimal timing of peripheral blood stem cell harvesting following priming with cyclophosphamide and G-CSF.	*Bone Marrow Transplantation* 2007; 40: 925–930.
Russell (2008)	Russell N, Mesters R, Schubert J, Boogaerts M, Johnsen HE, *et al.* A phase 2 pilot study of pegfilgrastim and filgrastim for mobilizing peripheral blood progenitor cells in patients with non-Hodgkin's lymphoma receiving chemotherapy.	*Haematologica* 2008; 93(3): 405-412.
Andreola (2012)	*Andreola G, Vanazzi A, Radice D, Babic A, Rabascio C, et al. Who should be really considered as a poor mobilizer in the plerixafor era?*	*Transfusion and Apheresis Science 2012; 47(1):27-32.*
Jagasia (2011)	Jagasia MH, Savani BN, Neff A, Dixon S, Chen	*Bone Marrow*

Study ID	Protocol title/ Publication title	Publication citation
	H *et al.* Outcome, toxicity profile and cost analysis of autologous stem cell mobilization.	*Transplantation* 2011; 46: 1084–1088.
Nazha (2011)	Nazha A, Cook R, Vogl DT, Mangan PA, Gardler M, *et al*. Stem cell collection in patients with multiple myeloma: impact of induction therapy and mobilization regimen.	*Bone Marrow Transplantation* 2011; 46: 59–63.
Hamadani (2012)	Hamadani M, Kochuparambil ST, Osman S, Cumpston A, Leadmon S, *et al.* Intermediate-dose versus low-dose cyclophosphamide and granulocyte colony-stimulating factor for peripheral blood stem cell mobilization in patients with multiple myeloma treated with novel induction therapies.	*Biology of Blood and Marrow Transplantation* 2012; 18: 1128–1135.
Milone (2013b)	Milone G, Tripepi G, Martino M, Ancora F, Bartolozzi B, *et al.* Early measurement of CD34+ cells in peripheral blood after cyclophosphamide and granulocyte colony-stimulating factor treatment predicts later CD34+ mobilisation failure and is a possible criterion for guiding "on demand" use of plerixafor.	*Blood Transfusion* 2013:11(1) 94-101.
Yang (2012)	Yang S-M, Chen H, Chen Y-H, Zhu H-H, Zhao T *et al.* The more, the less: age and chemotherapy load are predictive of poor stem cell mobilization in patients with hematologic malignancies.	*Chinese Medical Journal* 2012; 125(4): 593-598.
Pozotrigo (2013)	Pozotrigo M, Adel N, Landau H, Lesokhin A, Lendvai N, *et al.* Factors impacting stem cell mobilization failure rate and efficiency in multiple myeloma in the era of novel therapies: experience at Memorial Sloan Kettering Cancer Center.	*Bone Marrow Transplantation* 2013. doi: 10.1038/bmt.2012.281 [Epub ahead of print]
Vithanarachchi (2013) EHA poster	Vithanarachchi U, Bell J, Clark J, Braithwaite B, *et al.* Plerixafor is superior to conventional chemotherapy for first line stem cell mobilisation, and is effective even in heavily pre-treated patients.	Poster presented at EHA 2013.

8. Results of Trials

The PBAC recalled that it had previously considered that the claim of efficacy of plerixafor over the comparator was reasonable, but that the magnitude of benefit remained uncertain.

From data presented in the current re-submission for failed mobilisers, the PBAC noted that the mobilisation success rates varied across the plerixafor studies and the comparator studies. The PBAC noted that the mobilisation success rates appeared numerically higher for the plerixafor studies compared to the comparator studies, with the exception of the non-Hodgkin lymphoma population.

The current re-submission estimated incremental mobilisation success rates for use in the model as 6% for lymphoma failed mobilisers and 17% for multiple myeloma failed mobilisers. The PBAC noted that these estimates were lower than claimed in the previous re-submission (21% in the overall population).

From data presented in the current re-submission for rescue of failing mobilisers, the PBAC noted that there was more variability in the overall population's mobilisation success rates with plerixafor compared to the plerixafor failed mobilisers studies.

The PBAC noted that the economic evaluation applied the combined mobilisation success rates of 84% (95% CI 74%, 91%; n=9 datasets with 122 patients) for rescue of failing mobilisers with lymphoma. For multiple myeloma patients, the combined mobilisation success rate of 92% (95% CI 84%, 96%; n=8 datasets with 101 patients) was used in the economic model. This compared to the combined mobilisation success rate of 84% from the overall population applied to both lymphoma and multiple myeloma patients in the July 2012 re-submission.

The PBAC considered that the clinical data remained sparse, indirect and variable, but overall supported a claim of incremental benefit of plerixafor + G-CSF over G-CSF + chemotherapy. The number needed to treat (NNT) was in the range of 2-5.

No new data were presented in the re-submission in relation to comparative harms.

The PBAC noted recent updates to the TGA-approved plerixafor product information include information on reports of anaphylactic reactions, including anaphylactic shock, from the worldwide post-marketing experience. This is consistent with the recent changes to the US and European labels. Additional information on hyperleukocytosis and vasovagal reactions has also been included in the label overseas.

Important identified risks of plerixafor in the risk management plan are allergic reactions/hypersensitivity, orthostatic hypertension, syncope, postural syncope and syncope vasovagal, diarrhoea, nausea, vomiting, abdominal pain, and dizziness. Important potential risks include thrombocytopenia, interstitial lung disease, myocardial infarction, paraesthesia, engraftment failure, graft failure, tumour cell mobilisation (theoretical risk), splenomegaly, leukostasis, drug level NOS increased for patients with renal impairment, anxiety, hallucination, nightmare, and sleep disorder. Plerixafor has been associated with an increase in circulating leukaemia cells in some instances when given to patients with acute myeloid leukaemia and plasma cell leukaemia.

9. Clinical Claim

The re-submission described plerixafor in combination with G-CSF as superior compared to the current mobilisation regimens. The PBAC considered that for patients who had previously failed mobilisation this claim was adequately supported in terms of comparative efficacy, although the magnitude of benefit of plerixafor over the comparator remained difficult to quantify. The PBAC also considered that the claim was supported with respect the addition of plerixafor for patients who were failing chemotherapy plus G-CSF mobilisation.

10. Economic Analysis

The re-submission presented a modelled cost-effectiveness analysis based on data from the non-randomised and observational studies, using the proportion of patients successfully mobilised as the outcome.

The mobilisation success rates used in the previous and current re-submissions are presented in the table below.

Mobilisation success rates

	July 2012 re-submission		Current re-submission	
	Plerixafor	**Comparator**	**Plerixafor**	**Comparator**
Failed mobilisers				
Lymphoma	74%	53%	69%	63%
Multiple myeloma	74%	53%	81%	64%
Failing mobilisers (lymphoma)				
Successful mobilisation	84%	0%	84%	27.45%
Successful mobilisation on 2nd attempt	53%	53%	76.92%	63%
Failing mobilisers (multiple myeloma)				
Successful mobilisation	84%	0%	92%	27.45%
Successful mobilisation on 2nd attempt	53%	53%	76.92%	64%

Abbreviations: Chemo, chemotherapy; G-CSF, granulocyte-colony stimulating factor

The PBAC noted that with the exception of second mobilisation attempts, the incremental differences in success rates between treatments used in the current economic model were more conservative than in the July 2012 re-submission.

The model was a decision analysis applied separately for four patient populations:

- Failed mobilisers with lymphoma;
- Failed mobilisers with multiple myeloma;
- Rescue of failing mobilisers with lymphoma; and
- Rescue of failing mobilisers with multiple myeloma.

There were significant changes to the inputs of the economic evaluation compared to the July 2012 re-submission, as identified by the Economics Sub-Committee (ESC).

For failed mobilisers, the incremental cost per additional patient achieving successful mobilisation was between $105,000 and $200,000 for lymphoma patients and between $15,000 and $45,000 for myeloma patients. The PBAC noted that the difference was largely driven by the smaller incremental benefit between arms for lymphoma, coupled with higher incremental costs. The cost-offsets claimed for multiple myeloma patients were more than those for lymphoma patients.

For rescue of failing mobilisers the incremental cost per additional patient achieving successful mobilisation was between $15,000 and $45,000 for lymphoma patients and less than $15,000 for myeloma patients. The PBAC noted that the difference was again driven by the larger incremental cost-offsets claimed for multiple myeloma patients compared to lymphoma patients.

The re-submission calculated an overall ICER, weighted by estimated utilisation of between $15,000 and $45,000 per additional patient achieving successful mobilisation.

The overall incremental cost-effectiveness ratio was highest in Year 1 due to the 'prevalent' failed mobiliser population, who failed initial chemotherapy plus G-CSF, prior to plerixafor being listed on the PBS. These patients are "carried over" in Year 1 only. The model assumes that under the proposed listing, all patients who are failing a mobilisation with chemotherapy plus G-CSF will be captured under the rescue of failing mobilisers restriction from Year 1

onwards (i.e. peripheral blood CD34+ cell count ≤ 10 cells/μL or Day 1 CD34+ yield < 1.0 × 10^6 cells/kg).

The PBAC considered that the weighted ICER was an acceptable estimate and supported the cost-effectiveness of plerixafor.

11. Estimated PBS Usage and Financial Implications

The re-submission's estimate of the net cost to Government (re-calculated during the evaluation correcting for arithmetical errors in G-CSF cost-offsets and excluding apheresis AR-DRG) was less than $10 million over the first five years of listing.

The PBAC considered that there was considerable risk of leakage beyond the proposed PBS population into a lower risk population where the cost-effectiveness of plerixafor has not been established. The PBAC accepted the re-submission's proposed estimates of patient numbers as a reasonable upper limit of usage in line with the intended PBS population. The PBAC recommended that a risk sharing arrangement between the sponsor and the Government would be necessary to manage the risk of leakage, with a cap based on the re-submission's estimate of patient numbers.

12. Recommendation and Reasons

The PBAC recommended listing of plerixafor under the Section 100 Highly Specialised Drugs Program as an Authority Required (+/- Streamlined) benefit for use in combination with G-CSF, in patients with multiple myeloma or lymphoma requiring an autologous stem cell transplant who meet certain criteria. The recommendation was made on the basis of acceptable comparative effectiveness and cost-effectiveness over G-CSF + chemotherapy.

The PBAC recommended listing with a maximum quantity of 1 with 1 repeat, noting that one vial is sufficient for a single dose for patients weighing up to 100 kg. The PBAC noted the sponsor's claim that greater than 98% of transplant patients in Australia would weigh 100 kg or less. For patients weighing greater than 100 kg, prescribers would be able to request an increased maximum quantity from the Department of Human Services at the time of authority application.

The PBAC did not accept the restriction proposed by the re-submission due to concerns that it may encourage use mobilisation with plerixafor + G-CSF, rather than chemotherapy + G-CSF + plerixafor. The PBAC considered that a modified version of the restriction suggested by the Secretariat in July 2012 was more appropriate, namely:

- *Treatment, in combination with granulocyte-colony stimulating factor (G-CSF) in a patient with either lymphoma or myeloma who requires autologous stem cell transplantation and has failed previous stem cell collection.*
- *Treatment, in a patient with either lymphoma or myeloma who requires autologous stem cell transplantation and is undergoing chemotherapy plus G-CSF mobilisation, when the peripheral blood CD34 count is < 1.0 x 10^4/mL or <10 x 10^6/L on the day of planned collection, or when the first apheresis has yielded < 1.0 x 10^6 CD34+ cells/kg.*

The PBAC considered that the restriction should not limit use only to adult patients.

As previously the PBAC accepted that granulocyte-colony stimulating factor (G-CSF) in combination with chemotherapy (ifosfamide + carboplatin + etoposide for lymphoma; and cyclophosphamide for multiple myeloma) was the appropriate comparator.

The PBAC considered that the clinical data remained sparse, indirect and variable, but overall, supported a claim of incremental benefit of plerixafor + G-CSF over G-CSF + chemotherapy for failed mobilisers and for addition of plerixafor for patients failing G-CSF + chemotherapy mobilisation. The PBAC accepted that a high clinical need exists in small minority of patients, in whom the modelled incremental costs were acceptable given survival benefits of transplantation.

The PBAC considered that there was considerable risk of leakage beyond the proposed PBS population into a lower risk population where the cost-effectiveness of plerixafor has not been established. The PBAC accepted the re-submission's proposed estimates of patient numbers as a reasonable upper limit of usage in line with the intended PBS population. The PBAC recommended that a risk sharing arrangement between the sponsor and the Government would be necessary to manage the risk of leakage, with a cap based on the re-submission's estimate of patient numbers.

The PBAC noted the consumer comments received in relation to the submission for plerixafor from individuals (21), health care professionals (10) and organisations (2). The comments highlighted a number of perceived benefits of use of plerixafor including enabling more patients to proceed to transplantation, decreased pain and discomfort, and reducing anxiety associated with failing mobilisations.

In accordance with subsection 101(3BA) of the National Health Act 1953, the PBAC advised the Minister that it is of the opinion that, on the basis of the material available to it at its November 2013 meeting, plerixafor should not be treated as interchangeable on an individual patient basis with any other drug(s) or medicinal preparation(s).

The PBAC advised that plerixafor is not suitable for inclusion in the list of medicines for prescribing by nurse practitioners, as Section 100 listings are currently considered out-of-scope for prescribing by nurse practitioners.

The Safety Net 20 Day Rule does not apply to Section 100 listings.

Outcome:
Recommended

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
PLERIXAFOR			Mozobil	Sanofi-aventis
Plerixafor, 24 mg/1.2 mL injection: subcutaneous infusion, 1 x 1.2 mL vial	1	1		

Condition:	Mobilisation of haematopoietic stem cells

Restriction:	Section 100 (Highly Specialised Drugs Program) Public Hospital Authority Required (STREAMLINED) Private Hospital Authority Required
Clinical criteria:	The treatment must be in combination with granulocyte-colony stimulating factor (G-CSF) AND Patient must have lymphoma; OR Patient must have multiple myeloma AND Patient must require autologous stem cell transplantation AND Patient must have failed previous stem cell collection; OR Patient must be undergoing chemotherapy plus G-CSF mobilisation and their peripheral blood CD34+ count is less than 1.0 x 10^4/millilitre or less than 10 x 10^6/Lon the day of planned collection; OR Patient must be undergoing chemotherapy plus G-CSF mobilisation and the first apheresis has yielded less than 1.0 x 10^6 CD34+ cells/kg
Prescriber Instructions	Evidence that the patient meets the PBS restriction criteria must be recorded in the patient's medical records.
Administrative Advice	Note Applications for increased maximum quantities will only be authorised for patients with body weight greater than 100 kg

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

sanofi-aventis welcomes the PBAC's recommendation for plerixafor to be listed on the PBS, a decision which ensures equitable access to plerixafor for those patients who are unable (with conventional approaches) to mobilise sufficient peripheral blood stem cells to proceed to autologous stem cell transplantation.