PUBLIC SUMMARY DOCUMENT
Product: Plerixafor, solution for injection, 20 mg in 1 mL, 1.2 mL, Mozobil®
Sponsor: Genzyme Australasia Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

To request a S100 (Highly Specialised Drugs Program) Authority Required listing for use of plerixafor in mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous stem cell transplantation (ASCT) in patients with lymphoma and multiple myeloma who have failed previous stem cell collection attempts.

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 second consideration for this indication by the PBAC.

At the November 2010 meeting, the PBAC rejected a submission seeking a Section 100 (Highly Specialised Drugs Program) listing for use of plerixafor, in combination with granulocyte-colony stimulating factor (G-CSF), in mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL) and multiple myeloma (MM) who meet certain criteria.

For further details see the November 2010 Public Summary Document.

3. Registration Status

Plerixafor was registered by the TGA on 31 May 2010 for use in combination with 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 listing – Highly Specialised Drug program
Public and Private Hospital Authority Required

1. Patients with lymphoma who require ASCT and have failed previous stem cell collection attempts.
2. Patients with multiple myeloma who require ASCT and have failed previous stem cell collection attempts.

For PBAC's view, see Recommendation and Reasons.

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 granulocyte-colony stimulating factor (G-CSF) alone, or G-CSF with chemotherapy.

The submission proposed that the place in therapy of plerixafor is as second line therapy in combination with granulocyte-colony stimulating factor (G-CSF) in mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous stem cell transplantation (ASCT) for lymphoma and multiple myeloma patients who have failed previous attempts at stem cell collection because they were unable to collect the minimum $CD34^+$ cell yield for transplant ($2x10^6$ $CD34^+$ cells/kg) or were unable to proceed to apheresis because of low peripheral blood $CD34^+$ cell counts.

6. Comparator

The submission nominated G-CSF in combination with chemotherapy (ifosfamide + carboplatin + etoposide for lymphoma; and cyclophosphamide for multiple myeloma) as the comparator in treating patients with lymphoma and multiple myeloma who have failed previous stem cell collection attempts. This was as previously agreed by the PBAC.

7. Clinical Trials

The basis of the re-submission was two arms of a retrospective study using plerixafor plus G-CSF and chemotherapy plus G-CSF (Pusic, 2008); five observational studies of patients receiving plerixafor plus G-CSF (Calandra, 2008; Fowler, 2009; Micallef, 2009; Tricot, 2010; Duarte, 2011); one arm of a non-randomised study of patients receiving chemotherapy plus G-CSF (Majado, 2003); one observational study of patients receiving chemotherapy plus G-CSF (McKibbin, 2007); and one arm of a retrospective study using chemotherapy plus G-CSF (Goterris, 2005) in patients who have failed previous stem cell collections.

For PBAC's view, see Recommendation and Reasons.

The following trials had been published at the time of submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
Retrospective study (includes chemotherapy plus G-CSF and plerixafor plus G-CSF)		
Pusic I et al	Impact of Mobilisation and Remobilisation Strategies on Achieving Sufficient Stem Cell Yields for Autologous Transplantation.	Biology of Blood and Marrow Transplantation 2008; 14:1045-1056.
Plerixafor plus G-CSF		
Calandra G et al	AMD3100 plus G-CSF can successfully mobilise CD34+ cells from non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma patients previously failing mobilisation with chemotherapy and/or cytokine treatment: Compassionate use data.	Bone Marrow Transplantation 2008; 41:331-338.
Fowler CJ et al	Rescue from failed growth factor and/or chemotherapy HSC mobilisation with G-CSF and plerixafor (AMD3100): An institutional experience.	Bone Marrow Transplantation 2009; 43:909-917
Micallef I et al	Successful stem cell remobilization using plerixafor (Mozobil) with non-Hodgkin Lymphoma: Results from the plerixafor NHL Phase 3 study rescue protocol.	Biology of Blood and Marrow Transplantation 2009; 15: 1578-86.
Tricot G et al	Safety and efficacy assessment of plerixafor in patients with multiple myeloma proven or predicted to be poor mobilisers, including assessment of tumor cell mobilisation.	Bone Marrow Transplantation 2010; 45:63-68.
Duarte RF et al	Plerixafor plus granulocyte CSF can mobilize hematopoietic stem cells from multiple myeloma and lymphoma patients failing previous mobilization attempts: EU compassionate use data.	Bone Marrow Transplantation 2011; 46(1): 52-8.

Trial ID / First author	Protocol title / Publication title	Publication citation
Chemotherapy plus G-CSF		
Majado MJ et al	Second mobilization of peripheral blood progenitor cells in patients with poor first mobilization.	Transplantation Proceedings 2003; 35(5): 2027-8
McKibbin T et al	Paclitaxel and filgrastim for hematopoietic progenitor cell mobilization in patients with hematologic malignancies after failure of a prior mobilization regimen.	Leukemia and Lymphoma 2007; 48(12): 2360-6.
Goterris R et al	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(10): 847-53.

Abbreviations: G-CSF, granulocyte-colony stimulating factor; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PB, peripheral blood; US, United States

8. Results of Trials

The table below summarises the number of patients who achieved the minimum number of CD34+ cells required for transplantation during re-mobilisation. Transplantation using pooled cells from other collections was allowed in most studies. The numbers of patients achieving minimum target cell collections with pooling were extracted from the relevant publications during the evaluation. The proportions of patients achieving the minimum target with pooling are higher compared to the proportion of patients achieving the minimum target without pooling.

Patients achieving ≥ 2 x 10^6 CD34+ cells/kg

	Lymphoma		MM	Total population (no pooling)	Total population (with pooling)
	NHL	HL			
Plerixafor plus G-CSF, n/N (%)					
Calandra (2008)	*38/63 (60)*	*13/17 (77)*	25/35 (71)	76/115 (66)	NR
Fowler (2009)	*10/10 (100)*	*1/2 (50)*	6/6 (100)	18/20 (90)	18/20 (90)
Micallef (2009)	37/62 (60)	NA	NA	37/62 (60)	NR
Pusic (2008)	NR	NR	NR	13/18 (72)	15/18 (83)
Tricot (2010)	NA	NA	15/20 (*75*)	15/20 (75)	NR
Duarte (2011)	15/24 (63)		27/32 (84)	42/56 (75)	NR
Combined mean	**114/178 (64)**		**73/93 (78)**	**201/291 (69)**	**33/38 (87)**
Chemotherapy plus G-CSF, n/N (%)					
Majado (2003)	NR	NR	NR	4/8 (50)	4/8 (50)
McKibben (2007)	4/17 (24)	NA	2/7 (29)	7/26 (27)	17/26 (65)
Goterris (2005)	NR	NR	NR	21/41 (51)	31/41 (76)
Pusic (2008)	NR	NR	NR	9/34 (26)	18/34 (53)
Combined mean	**4/17 (24)**		**2/7 (29)**	**41/109 (38)**	**70/109 (64)**

Abbreviations: HL, Hodgkin lymphoma; MM, multiple myeloma; NA, not applicable; NHL, non-Hodgkin lymphoma; NR, not reported

The PBAC considered that results obtained by application of the minimum threshold to the pooled cell numbers is more applicable to Australian clinical practice, as pooling of cells is standard practice in Australia. The percentage of patients achieving greater than or equal to 2×10^6 CD34+ cells/kg from Pusic (2008) yields a total population (with pooling) of 83% (Plerixafor + G-SCF) versus 53% (Chemo+G-SCF). However, the results using the combined mean of Pusic (2008) and the five observational studies are 87% versus 64% respectively, which may be a more appropriate basis for comparison.

Lymphoma

The proportion of patients with lymphoma receiving plerixafor and achieving greater than or equal to 2×10^6 CD34+ cells/kg ranged from 60% to 92%.

Two studies provided data for NHL and HL separately (Calandra, 2008; Fowler, 2009). There were no consistent trends for differences in response for the two diseases, although numbers in the HL cohorts were small.

For chemo-mobilisation, 4 out of 17 (24%) of NHL patients from McKibben (2007) successfully achieved greater than or equal to 2×10^6 CD34+ cells/kg during the second collection. However, if the combined collection was considered, the proportion of NHL patients who successfully collect greater than or equal to 2×10^6 CD34+ cells/kg increases to 65% (11/17).

Multiple myeloma

The proportion of patients receiving plerixafor plus G-CSF collecting greater than or equal to 2×10^6 CD34+ cells/kg ranged from 71% to 100%.

For chemo-mobilisation, 2 of 7 (29%) MM patients achieved greater than or equal to 2×10^6 CD34+ cells/kg during the second collection attempt (derived from McKibben, 2007). If the combined collection is considered, the proportion of patients who successfully collect greater than or equal to 2×10^6 CD34+ cells/kg is substantially higher, i.e. 57% (4/7) patients.

Total population (no pooling)

The proportion of patients achieving greater than or equal to 2×10^6 CD34+ cells/kg in the total population (no pooling) of patients receiving plerixafor for the second mobilisation ranged from 60% to 90%. This population included patients with other diagnoses e.g. leukaemia.

For chemo-mobilisation, the proportion of patients achieving the minimum collection for the total population ranged from 26% to 51%. The re-submission attributed the range of results to the heterogeneity of the populations. However, the substantial variation in the results for the total population undergoing chemo-mobilisation highlights the uncertainty surrounding the estimate, particularly given that the re-submission used the results from the lower end of the reported range to inform the economic evaluation.

Total population (with pooling previous mobilisation attempts)

The proportion of patients treated with plerixafor achieving greater than or equal to 2×10^6 CD34+ cells/kg ranged from 83% to 90% with pooling of cells; compared to 60% to 90% for second mobilisation attempt only.

For chemo-mobilisation, the data on the proportions of patients successfully mobilising the minimum collection with pooling are more consistent with the reporting for Majado (2003) and McKibben (2007). Of the failed mobilisers undergoing chemo-mobilisation, 50% to 76% of patients achieved the minimum number of cells with pooling of cells from previous collections. This was substantially higher than the proportions of patients who collect the minimum target cells during the second mobilisation attempt only (26% to 51%).

Transplantation using pooled cells from other collections was allowed in most studies, thus the proportion of patients proceeding to transplantation was often higher than the proportion

of patients achieving the target cell yield after re-mobilisation. The table below summarises the data on the proportion of patients proceeding to transplantation.

Patients proceeding to transplantation

	Lymphoma n/N (%)		MM n/N (%)	Total population n/N (%)
	NHL	HL		
Plerixafor plus G-CSF				
Calandra (2008)	*45/63 (71)*	*15/17 (88)*	27/35 (77*)*	87/115 (76)
Fowler (2009)	*9/10 (90)*	*1/2 (50)*	5/6 (83)	17/20 (85)
Micallef (2009)	52/62 (84)	NA	NA	52/62 (84)
Pusic (2008)	NR	NR	NR	15/18 (83)
Tricot (2010)	NA	NA	17/20 (85)	17/20 (85)
Duarte (2011)[c]	NA		NA	NA
Chemotherapy plus G-CSF				
Majado (2003)	NR	NR	NR	NR
McKibben (2007)	NR	NA	NR	16/26 (62)
Goterris (2005)	NR	NR	NR	23/41 (56)
Pusic (2008)	NR	NR	NR	18/34 (53)

Abbreviations: HL, Hodgkin lymphoma; MM, multiple myeloma; NA, not applicable; NHL, non-Hodgkin lymphoma; NR, not reported

For the total population, 76% to 85% of patients receiving plerixafor proceeded to transplantation. The re-submission claimed that 53% to 62% of patients undergoing chemo-mobilisation proceeded to transplantation.

Overall, plerixafor appears to increase the number of patients proceeding to transplantation compared to chemo-mobilisation; but the magnitude of the benefit is unclear as estimates are from small non–randomised and uncontrolled studies.

The median days of apheresis for most observational cohorts receiving plerixafor ranged from 2 to 3 days, with the exception of 7 days in Tricot (2010). For the comparator of chemo-mobilisation, the median number of days of apheresis ranged from 2 to 3 days.

Pusic (2008) was the only study which facilitated a point of comparison of the number of days of apheresis with the two mobilisation strategies. The median number of apheresis days was longer for plerixafor-treated patients (2.5 days) versus patients undergoing chemo-mobilisation (2 days) in Pusic (2008).

The re-submission presented new toxicity data from Duarte (2011) on plerixafor; and for chemo-mobilisation from McKibben (2007) and Goterris (2005). The most common adverse events reported for plerixafor in the trials and studies include gastrointestinal disorders (diarrhoea, nausea), injection site reactions (erythema, pruritis) and dizziness. The additional safety data from Duarte (2011) are consistent with this pattern of adverse events.

For chemo-mobilisation, there were reports of febrile neutropenia leading to hospitalisation, anaemia (some requiring transfusion), and thrombocytopenia in McKibben (2007). One patient developed sepsis resulting in death. However, the dose of paclitaxel used was higher than the maximum dose recommended in the PI. The adverse events reported by Goterris (2005) were likely to be related to the high dose chemotherapy (HDT) supported by ASCT, and were not directly comparable to adverse events related to chemo-mobilisation.

9. Clinical Claim

The re-submission claimed that plerixafor, administered in conjunction with G-CSF, can be an effective means to salvage patients who have previously failed standard [peripheral blood stem cell] mobilisation attempts. The re-submission also claimed that plerixafor is generally safe and well-tolerated.

The PBAC considered that there was a lack of comparator data available to quantify the extent of the benefit of plerixafor over chemo-mobilisation. The PBAC noted that the results for chemo-mobilisation may not be representative of current clinical practice and may underestimate the efficacy of chemo-mobilisation.

In regard to safety, the PBAC considered the claim was reasonable if plerixafor plus G-CSF was used instead of chemo-mobilisation. However, it was difficult to quantify the rate of febrile neutropenia and transfusion-related interventions from chemo-mobilisation based on the supporting data provided. No long-term safety data was presented.

10. Economic Analysis

An updated modelled economic evaluation was presented.

For PBAC's view, see Recommendation and Reasons.

The structure of the model was the same as for failed mobilisers in the November 2010 submission, which was a decision analysis applied separately for the lymphoma and MM population. The re-submission presented an incremental cost per successful mobilisation (Step 1 of the stepped economic evaluation). The base-case presented was a cost-utility analysis (Step 3 of the stepped economic evaluation).

The results for Step 1 of the economic evaluation produced an incremental cost per additional patient achieving successful mobilisation between $15,000 and $45,000 in lymphoma patients and less than $15,000 in MM patients.

The incremental cost per additional successful mobilisation is lower for MM patients, because of the additional costs associated with the comparator for treating the adverse event of febrile neutropenia with cyclophosphamide (not included in lymphoma) and the greater incremental benefit, compared with lymphoma. No cost-offsets are claimed for ICE salvage chemotherapy and subsequent risk of febrile neutropenia for lymphoma patients.

Sensitivity analyses of Step 1 for lymphoma and MM patients were conducted during the evaluation with alternative estimates.

The results of the sensitivity analyses indicated that the incremental cost per additional successful mobilisation for the lymphoma population was sensitive to the proportion of patients that successfully mobilise (particularly for chemo-mobilisation), the number of days of apheresis, the number of vials of plerixafor per day, and the claimed cost offset from the differing number of days of G-CSF pre-apheresis between arms.

The results of the sensitivity analyses indicated that the incremental cost per additional successful mobilisation for the MM population was sensitive to the proportion of patients that successfully mobilise, the risk of neutropenia and associated costs, the number of days of apheresis and the number of vials of plerixafor per day.

The results for Step 3 of the economic evaluation produced an incremental cost per quality-adjusted life year (QALY) gained between $15,000 and $45,000 for lymphoma patients and between $45,000 and $75,000 for MM patients.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The net financial cost to the PBS was estimated by the submission to be less than $10 million per year in Year 5. The estimate was considered uncertain.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC noted that the intent of requested restriction is to include patients who have failed previous attempts at peripheral blood stem cell collection as well as those who are currently failing, i.e. "immediate rescue", which was acknowledged by the sponsor in its Pre-PBAC Response. Therefore, the restriction would be required to accommodate the different populations.

As previously agreed, the PBAC accepted the comparators for this submission, G-CSF in combination with chemotherapy (ifosfamide +, carboplatin + etoposide for lymphoma and cyclophosphamide for multiple myeloma) in patients who have failed previous stem cell collection attempts.

The PBAC considered that the clinical management algorithm presented in the submission did not adequately represent current clinical practice in Australia. The PBAC expected that it would be more similar to the clinical algorithm presented by Herbert at al (2011). In this algorithm, plerixafor is used pre-emptively for predicted poor mobilisers, as well as immediate salvage where the yield of CD34+ cells for patients undergoing apheresis is considered to be suboptimal. The PBAC noted that minimal data are presented in the submission for the "immediate rescue" population.

New data for plerixafor plus G-CSF presented in this re - submission are from Duarte (2011), as identified during the evaluation and presented in the November 2010 Commentary, and additional data from Tricot (2010) due to the extension of the definition of a "failure" in the re-submission. Three additional studies of patients receiving chemotherapy plus G-CSF (comparator) are also presented in the re-submission (Majado, 2003; McKibben, 2007; Goterris, 2005). The PBAC noted that the evidence presented in the re-submission to support the requested listings is derived from non-randomised studies (often data from one arm of the study) and observational cohorts and that these studies may be subject to bias (e.g. selection bias) and confounding.

The PBAC considered that results obtained by application of the minimum threshold to the pooled cell numbers is more applicable to Australian clinical practice, as pooling of cells is standard practice in Australia. The PBAC noted that the percentage of patients achieving greater than or equal to $2x10^6$ CD34+ cells/kg from Pusic (2008) yields a total population (with pooling) of 83% (Plerixafor + G-SCF) versus 53% (Chemo+G-SCF). However, the results using the combined mean of Pusic (2008) and the five observational studies are 87% versus 64% respectively, which may be a more appropriate basis for comparison.

The PBAC noted the economic model in the resubmission is based on mobilisation success rates (ie proportion of patients achieving greater than or equal to 2 x 10^6 CD34+ cells/kg). The PBAC considered that patients proceeding to transplant was the more relevant outcome, noting that the incremental benefit of plerixafor using mobilisation success data (40% lymphoma; 49% MM) is higher than if the proportion of the total population proceeding to transplant is used (14-32%).

The PBAC noted the main economic uncertainties. It further considered that the greatest uncertainties remain around the assumed survival benefits accruing from additional lymphoma and myeloma patients proceeding to autologous transplantation. The PBAC noted that the transplant benefit data for lymphoma are out of date as they pre-date use of rituximab, inclusion of which is considered standard care for patients with B-cell lymphoma, particularly diffuse large B-cell lymphoma. The PBAC also noted that the modelled greatest gains in life years for lymphoma patients treated with plerixafor compared to chemo-mobilisation is during the relapse health state (incremental life years gained 0.849) rather than the remission health state (incremental life-years gained 0.649), which is implausible. Taken together with the other key issues highlighted in the ESC advice, these matters meant that steps 2 and 3 of the economic evaluation are very uncertain.

The PBAC considered that the incremental cost per quality-adjusted life year (QALY) gained between $15,000 and $45,000 for lymphoma patients and between $45,000 and $75,000 for MM patients are highly uncertain due to the considerable uncertainty associated with the economic model. Unlike Step 1, where incremental costs are lower per additional successful mobilisation in myeloma patients, the incremental cost per QALY gained is lower in lymphoma patients than myeloma patients. This is predominately due to the larger apparent QALY gains during the remission and relapse health states, which are largely driven by the modelled greater gain in life years for lymphoma patients (based on NHL data) compared to MM patients.

The PBAC considered that there is major uncertainty arising from the low quality of clinical data about the incremental numbers of patients proceeding to transplant and from the attempt to translate these increments into life years gained (LYG). The latter requires many highly uncertain assumptions and the PBAC considered that collectively these render the model inappropriate. As stated in the November 2010 PBAC Minutes, a simple and conservative comparison of costs of mobilisation on a per patient basis should also be provided, rather than a claim of highly uncertain transplant benefits.

The PBAC therefore rejected the submission on the basis of a high and uncertain cost-effectiveness ratio.

The PBAC also acknowledged and noted the consumer comments on this item.

Recommendation:
Reject

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

Genzyme is disappointed by the decision but is committed to continuing to work with the PBAC to ensure that Mozobil is made available on the PBS for eligible patients with lymphoma and multiple myeloma.