PUBLIC SUMMARY DOCUMENT
Product: Plerixafor, solution for subcutaneous injection, 20 mg per mL, 1.2 mL, Mozobil®
Sponsor: Genzyme Australasia Pty Ltd
Date of PBAC Consideration: November 2010

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drugs Program) listing for use 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.

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 drug had not previously been considered by the PBAC.

3. Registration Status

Plerixafor was TGA registered on 31 May 2010 for use in combination with G-CSF to mobilise haematopoietic stem cells 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
Private Hospital Authority Required

1. Patients with NHL who are undergoing ASCT and have not failed previous stem cell collections or collection attempts.
2. Patients with MM who are undergoing ASCT, have not failed previous stem cell collections or collection attempts, and are predicted to be poor mobilisers.
3. Patients with NHL/HL who are undergoing ASCT and have failed previous stem cell collections or collection attempts.
4. Patients with MM who are undergoing ASCT and have failed previous stem cell collections or collection attempts.

'Failure' is defined as the inability to collect the minimum number of cells required for transplantation (2×10^6 $CD34^+$cells/kg).

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

High dose chemotherapy with autologous stem cell transplantation is an 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.

The submission claimed that plerixafor used in combination with G-CSF would provide an alternative therapy to enhance mobilisation of stem cells in patients with NHL, HL and MM who are undergoing high dose chemotherapy plus autologous stem cell transplantation (ASCT).

6. Comparator

The submission nominated G-CSF alone as the comparator in treating patients with NHL and MM, who have not failed previous stem cell collections or collection attempts. The PBAC did not accept G-CSF alone as the appropriate comparator.

The submission nominated G-CSF in combination with chemotherapy (ifosfamide plus carboplatin plus etoposide for NHL; and cyclophosphamide for MM) as the comparator in treating patients with NHL, HL and MM, who have failed previous mobilisation attempts. The PBAC considered this appropriate.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

For use as first-line therapy in NHL, the submission presented one randomised trial comparing first-line plerixafor plus G-CSF with placebo plus G-CSF in NHL patients (Study 3101).

For use as first-line treatment in predicted poor mobilisers with MM, the submission presented one randomised trial comparing first-line plerixafor 0.24 mg per kg plus G-CSF with placebo plus G-CSF in MM patients, with *post-hoc* analyses in the subgroup defined as predicted poor mobilisers (i.e. MM patients with a pre-apheresis peripheral blood CD34+ count less than 10 cells per microlitre) (Study 3102).

For second-line use in patients with NHL, HL and MM, the submission presented five observational cohorts of patients receiving second-line plerixafor 0.24 mg per kg plus G-CSF in NHL, HL and MM patients (Calandra 2008, Fowler 2009, Micallef 2009, Pusic 2008 and Tricot 2010); and compared these to one observational cohort of patients receiving second-line chemotherapy plus G-CSF (Pusic 2008). An independent search located an additional observational cohort of NHL, HL and MM patients receiving second-line plerixafor (Duarte 2010). Details these trials are presented in the following table.

Trial ID / First author	Protocol title / Publication title	Publication citation
First-line therapy in NHL		
plerixafor plus G-CSF vs. placebo plus G-CSF		
Study 3101 DiPersio et al. (2009a)	Phase III prospective randomised double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilisation and transplantation for patients with non-Hodgkin's lymphoma	*Journal of Clinical Oncology* 27:4767-4773, 2009

DiPersio et al. (2007)	A phase III, multicenter, randomised, double-blind, placebo-controlled, comparative trial of AMD3100 (Plerixafor)+G-CSF vs. placebo+G-CSF in non-Hodgkin's lymphoma (NHL) patients for autologous haematopoietic stem cell (aHSC) transplantation	*Blood* (ASH Annual Meeting Abstracts) 2007; 110: Abstract 601
First-line therapy in MM		
plerixafor plus G-CSF vs. placebo plus G-CSF		
Study 3102 DiPersio et al. (2009b)	Plerixafor and G-CSF versus placebo and G-CSF to mobilise haematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma.	*Blood* 113:5720-5726, 2009
DiPersio et al. (2007)	A Phase III, Multicenter, Randomised, Double-Blind, Placebo-Controlled, Comparative Trial of AMD3100 (Plerixafor)+G-CSF vs. G-CSF+Placebo for Mobilisation in Multiple Myeloma (MM) Patients for Autologous Haematopoietic Stem Cell (aHSC) Transplantation	*Blood* (ASH Annual Meeting Abstracts) 2007; 110: Abstract 445
Second-line NHL, HL and MM (failed mobilisers)		
plerixafor plus G-CSF		
Calandra 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*, 41:331-338, 2008
Fowler et al.	Rescue from failed growth factor and/or chemotherapy HSC mobilisation with G-CSF and plerixafor (AMD3100): An institutional experience	*Bone Marrow Transplantation* 43:909-917, 2009
Micallef et al.	Successful Stem Cell Mobilisation Rescue by AMD3100 (Plerixafor)+G-CSF for Patients Who Failed Primary Mobilisation: Results from the Phase III (3101-NHL) Study	*Blood* (ASH Annual Meeting Abstracts) 2007; 110: Abstract 602
Pusic et al.	Impact of Mobilisation and Remobilisation Strategies on Achieving Sufficient Stem Cell Yields for Autologous Transplantation	*Biology of Blood and Marrow Transplantation* 14:1045-1056, 2008
Tricot 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* 45:63-68, 2008
Duarte et al.	Plerixafor plus granulocyte CSF can mobilise hematopoietic stem cells from multiple myeloma and lymphoma patients failing previous mobilisation attempts: EU compassionate use data.	*Bone Marrow Transplantation* , advance online publication 22 March 2010; doi:10.1038/bmt.2010.54
chemotherapy plus G-CSF		
Pusic et al.	Impact of Mobilisation and Remobilisation Strategies on Achieving Sufficient Stem Cell	*Biology of Blood and Marrow Transplantation*

	Yields for Autologous Transplantation	14:1045-1056, 2008

8. Results of Trials

First-line non-Hodgkin lymphoma (NHL):

The primary outcomes of Study 3101 were the percentage of patients able to mobilise greater than or equal to 5 x 10^6 CD34+ cells per kg in less than or equal to 4 days of apheresis; and achieve greater than or equal to 2 x 10^6 CD34+ cells per kg in less than or equal to 4 days of apheresis and have successful polymorphonuclear and platelet engraftment (European Medicines Agency (EMA)-specific composite endpoint).

The secondary outcomes and *post-hoc* analyses for Study 3101 were the proportions of patients achieving the optimum number of CD34+ cells of greater than or equal to 2 x 10^6 CD34+ cells per kg within 2 and 4 days of apheresis, and the number of days of apheresis required to reach greater than or equal to 2 x 10^6 CD34+ cells per kg.

The following table summarises the results of the primary efficacy outcomes for Study 3101 in NHL patients.

Results of primary efficacy outcomes for Study 3101 in NHL patients

Trial ID	Plerixafor n/N (%)	Placebo n/N (%)	Risk Difference (95% CI)	Relative Risk (95% CI)	Odds Ratio (95% CI)
% of patients able to mobilise greater than or equal to 5 x 10^6 CD34+ cells/kg in less than or equal to 4 days of apheresis					
Study 3101 (NHL)	89/150 (59.3)	29/148 (19.6)	0.40 (0.30, 0.50)	3.03 (2.13, 4.31)	*5.99 (3.56, 10.07)*
p-value			p<0.00001	p<0.00001	p<0.00001
% of patients achieving greater than or equal to 2 x 10^6 CD34+ cells/kg in less than or equal to 4 days of apheresis and having successful polymorphonuclear and platelet engraftment (EMA-specific composite endpoint)					
Study 3101 (NHL)	126/150 (84.0)	64/148 (43.2)	0.41 (0.31, 0.51)	1.94 (1.59, 2.37)	6.89 (4.00, 11.88)
p-value			p<0.00001	p<0.00001	p<0.00001

Abbreviations: CI, confidence interval; EMA, European Medicines Agency; NHL, non-Hodgkin lymphoma

Statistically significantly more NHL patients treated with plerixafor achieved the primary endpoint and the EMA-specific composite endpoint compared to patients in the placebo arm. However, it was noted in DiPersio et al. (2009a) that the failure rate in the placebo arm of the trial was higher than expected.

More plerixafor treated patients (90%; 135 of 150) proceeded to transplant compared with 55.4% of patients (82 of 148) in the placebo arm. However, the magnitude of this benefit remained uncertain due to the high unexplained rates of treatment failure in placebo-treated patients.

For patients proceeding to transplant there were no statistically significant differences in successful polymorphonuclear and platelet engraftment or graft durability between plerixafor and placebo treated patients. For all patients, there was no evidence of a difference in patient survival at 12 months between the two treatment groups, although it was noted that there were few deaths in either plerixafor or placebo treated arms at 12 months. Longer term data on progression-free survival and overall survival for this trial will not be available until 2014.

The key outcomes differ from those chosen for use in the economic model. The key outcomes of the trial related to the proportions of patients achieving the optimum number of CD34+ cells within a specified number of days. The proportion of patients achieving the minimum number of CD34+ cells (greater than or equal to 2×10^6 CD34+ cells per kg) was considered to be more important for this submission and to reflect clinical practice. *Post-hoc* analyses were conducted to determine the proportion of patients achieving this minimum target collection within two days, and the mean number of days of apheresis required to achieve this minimum target collection.

The following table summarises the results the secondary outcomes and *post-hoc* analysis for Study 3101 in NHL patients.

Results of key secondary efficacy outcomes and *post-hoc* analysis for Study 3101 in NHL patients

Trial ID	Plerixafor n/N (%)	Placebo n/N (%)	Risk Difference (95% CI)	Relative Risk (95% CI)	Odds Ratio (95% CI)
% of patients achieving greater than or equal to 2 x 10^6 CD34+ cells/kg in less than or equal to 4 days of apheresis					
Study 3101 (NHL)	130/150 (86.7)	70/148 (47.3)	0.39 (0.30, 0.49)	1.83 (1.53, 2.20)	7.24 (4.09, 12.82)
p-value			p<0.00001	p<0.00001	p<0.00001
Post-hoc analysis of the % of patients achieving greater than or equal to 2 x 10^6 CD34+ cells/kg in less than or equal to 2 days of apheresis					
Study 3101 (NHL)	119/150 (79.3)	NR	NR	NR	NR

Abbreviations: CI, confidence interval; EMA, European Medicines Agency; NHL, non-Hodgkin lymphoma

A statistically significantly higher proportion of NHL patients receiving plerixafor achieved a collection of greater than or equal to 2×10^6 CD34+ cells per kg in less than or equal to 4 days of apheresis compared to placebo (86.7% versus 47.3%). The results of a *post-hoc* analysis of the proportion of plerixafor-treated patients achieving a collection of greater than or equal to 2×10^6 CD34+ cells per kg in less than or equal to 2 days of apheresis showed that the proportions achieving this minimum target in less than or equal to 2 days was only slightly lower than that reported achieving this target in less than or equal to 4 days (79.3% versus 86.7%).

The results of a post-hoc analysis for Study 3101 in NHL patients showed that patients in the plerixafor arm required fewer days of apheresis compared to the placebo arm to achieve the target collection of greater than or equal to 2×10^6 CD34+ cell per kg: mean of 2.02 versus 3.29 days.

<u>First-line predicted poor mobilisers with multiple myeloma (MM)</u>:
The submission presented the full trial population results however, there were not directly relevant to the requested PBS listing, (i.e. MM patients who have not failed previous stem cell collections or collection attempts, and are predicted to be poor mobilisers) and are not represented here.

The submission presented data to establish that the clinical efficacy of plerixafor would be more apparent in the subgroup of patients who are predicted to be poor mobilisers. The results of the *post-hoc* subgroup analyses for these poor mobilisers incorporated in the economic model are summarised in the following table.

***Post-hoc* analyses of outcomes for a subgroup of MM patients with a pre-apheresis peripheral blood CD34+ count of <10cells/μL on Day 4 and the full trial population from Study 3102**

Population	Plerixafor	Placebo	Difference	p-value
% of patients able to mobilise greater than or equal to 2 x 10^6 CD34+ cells/kg in less than or equal to 4 days of apheresis, n/N (%)				
PB CD34+ less than 10 cells/mcL	25/27 (92.6)	21/30 (70.0)	22.6%	0.031
Full population	141/148 (95.3)	136/154 (88.3)	7.0%	0.031
Post-hoc analysis: % of patients able to mobilise greater than or equal to 2 x 10^6 CD34+ cells/kg in less than or equal to 2 days of apheresis, n/N (%)				
PB CD34+ less than 10 cells/mcL	25/27 (92.6)	13/30 (43.3)	49.3%	<0.001
Full population	139/148 (93.9)	121/154 (78.6)	15.3%	<0.001
Post-hoc analysis: Mean number of days of apheresis to mobilise greater than or equal to 2 x 10^6 CD34+ cells/kg (Range)				
PB CD34+ less than 10 cells/mcL	1.33 (1, 4)	2.70 (1, 4)	1.02 days	<0.001
Full population	1.1 (1, 3)	1.5 (1, 4)	0.5 days	<0.0001

Abbreviations: MM, multiple myeloma; PB = peripheral blood;

There were substantial differences in the proportions of plerixafor-treated patients achieving optimum cell targets (greater than or equal to 6×10^6 CD34+ cells per kg in less than or equal to 2 days) between the full population and the subgroup of poor mobilisers (71.6% versus 40.7%).

For the more clinically relevant minimum cell collection target of greater than or equal to 2×10^6 CD34+ cells per kg in less than or equal to 2 days, 92.6% in predicted poor mobilisers achieved this target versus 93.9% in the full trial population.

Second-line NHL, HL and MM:

The following table summarises the number of patients achieving the optimum number of CD34+ cells of greater than or equal to 2 x 10^6 CD34+ cells per kg, in the observational cohort studies.

Patients achieving greater than or equal to 2 x 10^6 CD34+ cells/kg

	NHL	HL	MM	Total population	
	Plerixafor n/N (%)	Plerixafor n/N (%)	Plerixafor n/N (%)	Plerixafor n/N (%)	Chemotherapy n/N (%)
Calandra (2008)	38/63 (60)	13/17 (77)	25/35 (71)	76/115 (66)	NA
Duarte (2010)+	15/24 (63)		27/32 (84)	42/56 (75)	NA
Fowler (2009)	10/10 (100)	1/2 (50)	4/6 (67)*	17/20 (85)	NA
Micallef (2009)	37/62 (60)	NA	NA	37/62 (60)	NA
Pusic (2008)	NR	NR	NR	13/18 (72)	9/34 (26)
Tricot (2010)	NA	NA	7/10 (70)	7/10 (70)	NA

Abbreviations: HL, Hodgkin lymphoma; MM, multiple myeloma; NA, not applicable;
NHL, non-Hodgkin lymphoma; NR = not reported
* Patient 1 and Patient 12 with MM failed mobilisation.
Note: Data for NHL/HL separated during the evaluation where possible. Some of the data were corrected for transcription errors. Data from Duarte 2010 were extracted during the evaluation
+ Duarte (2010) identified during the evaluation

NHL: In the pivotal trial Study 3101, 86.7% of NHL patients receiving plerixafor achieved the minimum collection of greater than or equal to 2×10^6 CD34+ cells per kg in less than or equal to 4 days in the first-line setting. Data from the subset of

observational cohorts reporting this outcome suggested that 60% to 100% of patients receiving plerixafor in the second-line setting achieved this minimum target collection.

HL: The pivotal direct randomised trials presented in the submission did not recruit HL patients. Based on small numbers of patients in the observational cohorts, 50% to 77% of the patients successfully mobilised the minimum target collection. The PBAC noted that the data for HL patients was very uncertain in that the data was non randomised and was based on very small patient numbers (n=19).

MM: In the pivotal trial Study 3102, 95.3% of MM patients from the full trial population receiving plerixafor achieved the minimum collection of greater than or equal to 2×10^6 CD34+ cells per kg in less than or equal to 4 days in the first-line setting. Data from the observational cohorts indicated that 67% to 84% of MM patients receiving plerixafor in the second-line setting achieved this minimum target collection.

There were limited data available to assess the impact of plerixafor in cell mobilisation in the second-line setting. However, plerixafor-treatment appeared to produce quantitatively similar results in achieving minimum cell targets (greater than or equal to 2×10^6 CD34+ cells per kg) in the first-line and second-line setting for NHL and MM.

Pusic et al (2008) was the only observational study to report cell collection for chemotherapy plus G-CSF mobilisation. Data were reported for all disease groups combined. Of 34 patients treated with chemotherapy-based mobilisation regimens, nine patients (24%) achieved the minimum cell collection of greater than or equal to 2×10^6 CD34+ cells per kg. There were limited data presented to assess the effectiveness of chemotherapy plus G-CSF in second-line mobilisation.

For PBAC's view of these results, see Recommendations and Reasons.

Based on the short-term trials and studies, the majority of the adverse events associated with plerixafor appeared to be mild to moderate; and included gastrointestinal disorders (e.g. diarrhoea, nausea, vomiting, flatulence and abdominal pain), injection site reactions (e.g. erythema and pruritis) and dizziness. There were no long term safety data available. Concerns regarding potential risk of mobilising tumour cells have been raised by regulatory agencies.

The PBAC noted the advice in the Pre-Subcommittee response that according to the TGA clinical evaluator, mobilisation of tumour cells can result from "all methods of mobilisation including G-CSF," and that the sponsor was currently undertaking long term follow-up studies of patients from the pivotal studies.

9. Clinical Claim

The submission claimed that plerixafor for first-line treatment is superior in terms of comparative effectiveness over placebo. No specific claim was made on the comparative safety of plerixafor plus G-CSF over G-CSF.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a stepped economic evaluation which was a cost-utility analysis.

The economic model was a decision analysis applied separately for each of four requested listings (NHL and HL second-line listings were considered together).

The results of Steps 1 to 3 of the economic evaluations for each of the requested indications are summarised in the following table, with incremental cost-effectiveness ratios shown in indicative ranges only.

Results of the economic evaluation

Indication	ICER
Step 1: Incremental cost per additional patient achieving successful mobilisation	
NHL (first-line and second-line)	$15,000 - $45,000
MM (first-line in predicted poor mobilisers and second-line)	$15,000 - $45,000
NHL/HL (second-line)	$15,000 - $45,000
MM (second-line)	< $15,000
Step 2: Incremental cost per life year gained	
NHL (first-line and second-line)	<$15,000
MM (first-line in predicted poor mobilisers and second-line)	$15,000 - $45,000
NHL/HL (second-line)	<$15,000
MM (second-line)	$15,000 - $45,000
Step 3: Incremental cost per QALY gained	
NHL (first-line and second-line)	$15,000 - $45,000
MM (first-line in predicted poor mobilisers and second-line)	$45,000 - $75,000
NHL/HL (second-line)	$15,000 - $45,00
MM (second-line)	$15,000 - $45,000

Abbreviations: HL, Hodgkin lymphoma; ICER, incremental cost-effectiveness ratio; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; QALY, quality adjusted life year

The submission claimed that plerixafor was more cost-effective in second-line only, than first- and second-line use; and in both first- and second-line use, and second-line only use, plerixafor was more cost-effective in NHL than in MM.

The economic model was most sensitive to the assumed event-free and overall survival; cost per vial of plerixafor; mobilisation success rate of plerixafor; and the rates of febrile neutropenia. The model was also sensitive to mobilisation success rate and survival estimates varied simultaneously.

The PBAC agreed that there was considerable uncertainty with the submission's economic evaluation. *See Recommendations and Reasons.*

11. Estimated PBS Usage and Financial Implications

The financial costs per year to the PBS (inclusive of patient co-payments) for the requested listings were all estimated in the submission to be less than $10 million.

The PBAC considered the submission's estimates uncertain.

12. Recommendation and Reasons

The PBAC noted that the submission nominated G-CSF alone as the comparator in treating patients with NHL and MM, who have not failed previous stem cell collections or collection attempts. However, the PBAC considered that the appropriate comparator for this indication was chemotherapy plus G-CSF as this was considered the most common

clinical practice for mobilisation in Australia. The PBAC noted that increased stem cell mobilisation can be obtained in combination with chemotherapy compared with G-CSF alone. In addition, chemotherapy is required as salvage for lymphoma and is commonly used routinely in myeloma patients, and therefore stem cell collection is incorporated with anti-lymphoma therapy and anti-myeloma therapy. The PBAC also noted that cyclophosphamide, when used for mobilisation in patients with multiple myeloma, is also a potent anti-myeloma therapy.

The PBAC thus agreed that G-CSF in combination with chemotherapy was the appropriate comparator for the treatment of patients with NHL, HL and MM, who have failed previous mobilisation attempts.

The PBAC noted that for use as first-line therapy in NHL, the submission presented one randomised trial comparing first-line plerixafor plus G-CSF with placebo plus G-CSF in NHL patients (Study 3101). Statistically significantly more NHL patients treated with plerixafor achieved the primary endpoint (59.3% versus 19.6%) and the EMA-specific composite endpoint (84.0% versus 43.2%) compared to patients in the placebo arm. The PBAC also noted that more plerixafor-treated patients (90%) proceeded to transplant compared with (55.4%) of patients in the placebo arm. However, the magnitude of this benefit remains uncertain due to the high unexplained rates of treatment failure in placebo-treated patients.

For use as first-line treatment in patients with MM who are predicted poor mobilisers, the submission presented Study 3102 comparing plerixafor plus G-CSF with placebo plus G-CSF, with post-hoc analyses in the subgroup defined as predicted poor mobilisers, (i.e. MM patients with a pre-apheresis peripheral blood CD34+ count of less than 10 cells per microlitre). The PBAC noted that there were only small differences in proportions of plerixafor-treated patients achieving the more clinically relevant minimum cell collection target of greater than or equal to 2×10^6 CD34+ cells per kg in less than or equal to 2 days (92.6% in predicted poor mobilisers versus 93.9% in the full trial population) which suggested that plerixafor is as effective in poor mobilisers at achieving minimum target cell collections.

For second-line use in patients with NHL, HL and MM, the submission presented five observational cohorts of patients receiving second-line plerixafor. The PBAC agreed that plerixafor treatment appeared to produce quantitatively similar results in achieving minimum cell targets (greater than or equal to 2 × 106 CD34+ cells per kg) in the first-line and second-line setting for NHL and MM. However, the PBAC noted that this was an uncontrolled series and as such there is a lack of comparator data and that the comparator data that do exist may not be representative as a consequence of reporting bias.

Regarding the clinical claim, the PBAC agreed that in the first-line mobilisation setting plerixafor plus G-CSF is superior in terms of comparative effectiveness over G-CSF alone but the clinical importance of this is uncertain in Australian practice as the submission did not provide a comparison with chemotherapy plus G-CSF. No specific claim was made on the comparative safety of plerixafor plus G-CSF over G-CSF.

For second-line treatment, the PBAC also agreed that plerixafor plus G-CSF could be an effective means to mobilise patients who have previously failed to mobilise, but noted

that the submission did not specifically make a claim regarding the comparative efficacy and safety over chemotherapy plus G-CSF.

The PBAC considered that as the submission did not provide any evidence of benefit over chemotherapy plus G-CSF in the first-line setting there was no basis for a cost-effectiveness comparison.

However, the PBAC noted that the submission presented a stepped economic evaluation which was a cost-utility analysis. The PBAC agreed that there is considerable uncertainty with the submission's economic evaluation, given the number of issues with the model and inputs as identified by its Economics Sub-Committee, such as the response rate of the comparator arms, risk of febrile neutropenia associated with chemotherapy-based mobilisation regimens, survival benefit associated with downstream treatment, and utilities/disutilities values.

The PBAC noted that the overall survival benefit modelled for plerixafor patients depended on an increased proportion of patients mobilising sufficiently to undergo autologous stem cell transplant (ASCT) and high dose chemotherapy (HDT), and the assumption that ASCT and HDT will improve overall survival compared to standard chemotherapy. The key trials presented in the submission reported survival data at 12 months, at which stage no difference in survival was apparent. The PBAC agreed that the extrapolation of the surrogate outcomes measured in the trials to a survival benefit in the economic model was highly uncertain. The PBAC also noted that the survival benefit studies considered in the submission would not have included patients who were poor mobilisers. There was also concern whether the economic model presented reflects likely clinical practice or outcomes in the Australian context and whether a comparison of survival benefit of chemotherapy plus G-CSF would be needed, as the incremental benefit of this combination may not be the same as G-CSF alone. The PBAC noted that longer term data on progression-free survival and overall survival for both these trials will not be available until 2014.

The PBAC therefore rejected the submission on the basis of an inappropriate comparator for the first-line indications, uncertain clinical benefit in second-line setting relating to the lack of comparative data, and uncertainty regarding the economic model.

The PBAC agreed that any future submission should provide a comparison with chemotherapy plus G-CSF in the first-line setting. 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 noted the advice of the Highly Specialised Drugs Working Party which concluded that plerixafor meets all the criteria for listing under the Highly Specialised Drugs Program.

The PBAC also noted the consumer comments received for 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 Australasia is committed to working to address the PBAC's issues and demonstrating, what Genzyme Australasia considers to be, the significant benefits of Mozobil for patients with lymphoma and multiple myeloma.