PUBLIC SUMMARY DOCUMENT
Product: Darbepoetin alfa, injection, 200 micrograms/0.4 mL, 300 micrograms/0.6 mL and 500 micrograms/1 mL, Aranesp® and Aranesp SureClick®
Sponsor: Amgen Australia Pty Ltd
Date of PBAC Consideration: November 2007

1. Purpose of Application

The submission sought to extend darbepoetin alfa's current Section 100 (Highly Specialised Drugs) PBS listing to include chemotherapy induced anaemia (CIA) in patients with non-myeloid malignancies 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

At the June 2003 PBAC meeting, the PBAC rejected a submission seeking PBS-listing of darbepoetin for CIA on the basis of uncertain clinical benefit and resultant uncertain and unacceptable cost-effectiveness. The PBAC had previously considered changes in the need for transfusion and improvements in quality of life (QoL) and survival to be the patient-relevant outcomes for drugs that stimulate erythropoiesis. There was no evidence of any survival gain, and any QoL gain was very small and not statistically significant. The PBAC considered that the economic model should have been based on a more patient relevant outcome, preferably QoL.

3. Registration Status

TGA registration for the three darbepoetin alfa products proposed for listing commenced on 7 June 2006. Darbepoetin alfa is indicated for the treatment of anaemia associated with chronic renal failure (CRF). Darbepoetin alfa is also indicated for the treatment of anaemia and reduction of transfusion requirements in patients with non-myeloid malignancies where anaemia develops as a result of concomitantly administered chemotherapy.

4. Listing Requested and PBAC's View

Private hospital authority required

Treatment of chemotherapy induced anaemia in patients with non-myeloid malignancies who satisfy all of the following criteria:

(1) Haemoglobin level of less than 100 g per L [alternative option: 110 g per L];
(2) At risk of requiring transfusion;
(3) Scheduled to receive at least a further 12 weeks of chemotherapy;
(4) Adequate iron stores as defined by iron studies.

Treatment with darbepoetin alfa should be administered according to a fixed dose regimen given every 3 weeks as described in the approved product information. The recommended starting dose is 500 micrograms.

Therapy should be continued for approximately 4 weeks after the end of chemotherapy or until haemoglobin concentrations approach 120 g per L.

A maximum of 6 packs per patient per course of chemotherapy will be PBS subsidised.

NOTE:
Haemoglobin levels and rate of change should be monitored regularly and if required the darbepoetin alfa dose adjusted or withheld according to the recommendations in the approved product information.

If the clinical response of the patient (fatigue, haemoglobin response) is inadequate after nine weeks, further therapy with darbepoetin alfa may not be effective.

This drug is not PBS-subsidised for treatment of anaemia in cancer patients who are not receiving concurrent chemotherapy.

For PBAC's view of the requested restriction, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Anaemia is defined as a deficiency in the concentration of haemoglobin-containing red blood cells (RBC) which deliver oxygen to the peripheral tissues to maintain the viability of cells.

In Australia, CIA requiring intervention is currently managed by red blood cells transfusion. Darbepoetin alfa has been shown to stimulate erythropoiesis in anaemic cancer patients, resulting in the correction and maintenance of haemoglobin. Darbepoetin would provide an alternative in the management of CIA.

6. Comparator

The submission nominated placebo or no pharmacological treatment as the comparator. This choice of comparator was previously accepted by the PBAC.

7. Clinical Trials

The submission presented seven new direct trials of darbepoetin alfa versus placebo:

- trials 114, 291(S1), 291 (S2), 232 and 145 are new placebo controlled trials, and
- trial 231 and trial 156 are new supplementary non- placebo controlled trials for the darbepoetin alfa 500µg every three week regimen.

The submission also re-presented trials 297 and 161 that were included in the previous submission.

The trials published at the time of submission were as follows:

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
Vansteenkiste J (Study 297)	Double-blind, placebo-controlled, randomised Phase 3 trial of darbepoetin alfa in lung cancer patients receiving chemotherapy.	J Natl Cancer Inst 2002;94(16):1211-20.
Tchemedyian S (Study 297)	The relationship between psychologic distress and cancer-related fatigue.	Cancer 2003;98:198-203.
Vansteenkiste J (Study 297)	Darbepoetin alfa in lung cancer patients on chemotherapy: a retrospective comparison of outcomes in patients with mild versus moderate-to-severe anaemia at baseline.	Supportive Care in Cancer 2004;12:253-62.

Hedenus M (Study 161) Littlewood T (Study 161	Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomised, double-blind, placebo-controlled study. Efficacy of darbepoetin alfa in alleviating fatigue and the effect of fatigue on quality of life in anaemic patients with lymphoproliferative malignancies.	British Journal of Haematology 2003;122:394-403. Journal of Pain and Symptom Management 2006;31:317-25.
Hedenus M (Study 114)	Randomised, dose-finding study of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies.	British Journal of Haematology 2002;119:79-86.
Kotasek D (Study 291(S1)	Darbepoetin alfa administered every 3 weeks alleviates anaemia in patients with solid tumours receiving chemotherapy; results of a double-blind, placebo-controlled, randomised study.	European Journal of Cancer 2003;39:2026-34.
Supplementary randomised trials		
Canon J-L (Study 231)	Randomised, double-blind, active-controlled trial of every-3-week darbepoetin alfa for the treatment of chemotherapy-induced anaemia,	Journal of the National Cancer Institute 2006;98:273-84.

Various applicability issues were noted:

- Several trials included patients whose anaemia was not predominantly due to chemotherapy;
- The inclusion criteria for most of the trials had a threshold for treatment of Hb 110g/L (different from proposed threshold of 100g/L).
- Most studies did not use the proposed dose of 500mcg every 3 weeks, and did not use the recommended duration of treatment. Studies 231 and 156 provide the only data for the proposed dose.

The endpoints used in the trials were highly variable. The definition of endpoints was also variable and as such a post hoc analysis of patient-level data was performed in the re-submission. It was agreed that the use of a post-hoc analysis was reasonable in this instance.

8. Results of Trials

A primary outcome used in the economic evaluation in the submission was the proportion of patients with transfusions from Week 1 to end of treatment period. The meta-analysis, based on post-hoc analyses of data, was used for the economic evaluation.

The key results from the post hoc analyses are summarised in the tables below.

Results of the *post-hoc* analysis of transfusion incidence (week 1 to end of treatment period) across the direct randomised trials

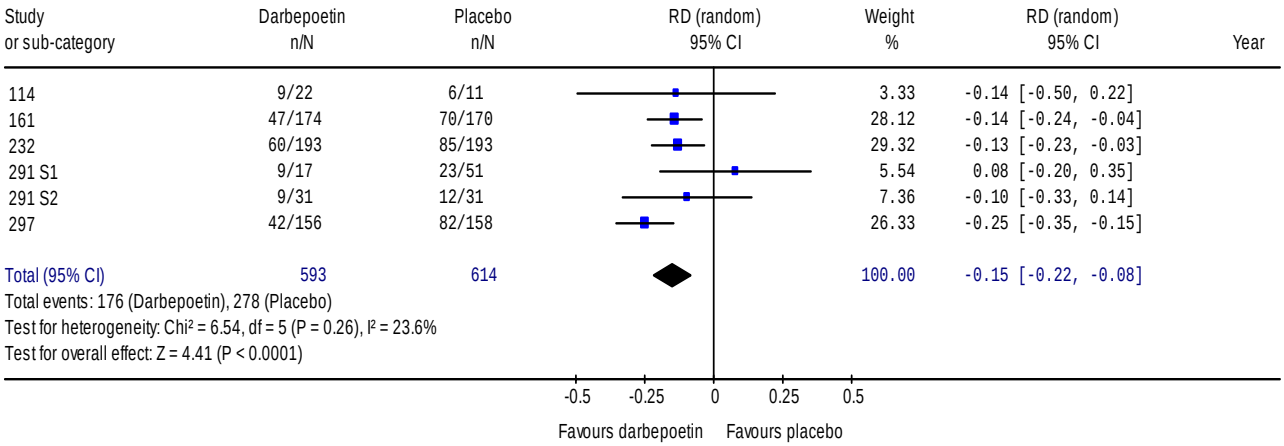
Trial ID	Darbepoetin alfa n with event/N (%)	Placebo n with event/N (%)	Relative risk (95% CI)
Trial 297	42/156(27%)	82/158(52%)	**0.52 (0.38, 0.70)**
Trial 161	47/174(27%)	70/170(41%)	**0.66 (0.48, 0.89)**
Trial 114	9/22(41%)	6/11(55%)	0.75 (0.36, 1.57)
Trial 291 (S1)	9/17(53%)	23/51(45%)	1.17 (0.68, 2.02)

Trial 291 (S2)	9/31(29%)	12/31(39%)	0.75 (0.37, 1.52)
Trial 232	60/193(31%)	85/193(44%)	**0.71 (0.54, 0.92)**
Pooled result (random effects)			**0.69 (0.56, 0.83)**
Chi-square for heterogeneity: 7.34 *P=0.20;* I^2 statistic with 95% uncertainty interval = 31.9%			
Trial 145 (Trial report values)	52/298(17%)	116/298(39%)	**0.45 (0.34, 0.60)**

Bolded typography indicates statistically significant differences between treatment groups

Transfusion incidence (week 1 to EOTP), meta-analysis of direct trials

Review: Darbepoetin vs placebo (Version 01)
Comparison: 02 Red blood cell transfusions
Outcome: 01 Transfusions during treatment (w1-EOT)



Results of the post-hoc analysis and the meta-analysis of the primary outcome, transfusion incidence (week 1 to end of treatment period), across the direct randomised trials showed that there was a significant reduction in the relative risk of receiving a transfusion in the darbepoetin group.

The number of units transfused was very marginally significantly lower in the darbepoetin versus the placebo group, and based primarily on the results of one trial (297). The PBAC considered this outcome was likely to have had very minimal clinical significance.

Results of the *post-hoc* analysis of number of units transfused per patient across the direct randomised trials

Trial ID	Darbepoetin alfa		Placebo		Mean difference (95% CI)
	N	mean (SD)	N	mean (SD)	
Trial 297	156	0.96(1.93)	158	2.00(2.92)	**-1.04 (-1.59, -0.49)**
Trial 161	174	1.87(4.53)	170	2.02(3.58)	-0.15 (-1.01, 0.71)
Trial 114	22	2.59(5.13)	11	2.91(3.30)	-0.32 (-3.22, 2.58)
Trial 291(S1)	17	2.47(3.30)	51	1.73(2.63)	0.74 (-0.99, 2.47)
Trial 292(S2)	31	0.94(1.81)	31	1.32(2.00)	-0.38 (-1.33, 0.57)
Trial 232	193	1.32(2.45)	193	2.04(3.35)	**-0.72 (-1.31, -0.13)**
Pooled result (random effects)					**-0.60 (-0.99, -0.21)**
Chi-square for heterogeneity: 6.15 *P=0.29;* I^2 statistic with 95% uncertainty interval =18.7%					

Bolded typography indicates statistically significant differences

Another outcome used in the economic evaluation in the submission is change in haemoglobin (Hb). A meta-analysis based on post-hoc analyses of data, was used for this economic evaluation.

Results of the *post-hoc* analysis of change in Hb (baseline to end of treatment period) across the direct randomised trials

Trial ID	Darbepoetin alfa		Placebo		Mean difference (95% CI)
	N	Mean (SD)	N	Mean(SD)	
Trial 297	155	1.06 (1.93)	154	0 (*1.52*)	**1.06 (0.67, 1.45)**
Trial 161	171	1.99 (2.08)	170	0.51 (1.34)	**1.48 (1.11, 1.85)**
Trial 114	22	1.77 (1.26)	11	0.89 (0.98)	**0.88 (0.10, 1.66)**
Trial 291 (S1)	17	1.23 (1.60)	51	0.44 (1.42)	0.79 (-0.06, 1.64)
Trial 292 (S2)	31	0.88 (1.50)	30	0.33 (1.14)	0.55 (-0.12, 1.22)
Trial 232	192	1.25 (1.52)	191	0.58 (1.39)	**0.67 (0.38, 0.96)**
Pooled result (random effects)					**0.94 (0.62, 1.27)**
Chi-square for heterogeneity: 13.23 *P=0.02;* I^2 statistic with 95% uncertainty interval =62.2%					

Bolded typography indicates statistically significant differences between treatment groups

The PBAC considered that a mean difference of less than one g/dL (10 g/L) of Hb is unlikely to be clinically significant.

A sub-group analysis of the population with baseline Hb < 100 g/L was performed to apply the randomised comparative trial evidence to the requested restriction. In the sub-group analysis, the incidence of transfusion during treatment was significantly less in the darbepoetin group than in the placebo group, but the number of red blood cell transfusions per transfused patient was not significantly different across the two groups.

Hb change from baseline to end of treatment period	Weighted mean difference (95% CI)
Hb < 100 g/L	
Meta-analysis of subgroup using random effects model	**0.93 (0.67, 1.19)**

As in the previous submission, there were no statistically significant improvements in quality of life measurements related to fatigue.

The primary endpoint in trial 145 was survival. In this study, median survival time (time to death) was 40 weeks for both darbepoetin and placebo patients, and the hazard ratio was 0.93 (95% CI: 0.78, 1.11).

Study 231 was a parallel group, double-blind direct comparison of the proposed darbepoetin dosing regimen with the weekly regimen (2.25mcg/kg) used in many of the other studies. The primary endpoint was percentage of subjects with RBC transfusion from week 5 to end of study. At baseline, 50% of the patients had Hb ≥ 100 g/L (above the proposed threshold). Both efficacy and toxicity endpoints were not significantly different between dosage regimens.

The re-submission also presented new toxicity data for the new trials. The key results are summarised below.

Overview of adverse events in the direct trials

Trial ID	Tx group	Adverse Events		Treatment-Related Adverse Events			Withdraw due to AEs	Deaths On-Trial
		Severe	Serious	Any	Severe	Serious		
Trial 297	DA	69/155 (45%)	60/155 (39%)	13/155 (8%)	4/155 (3%)	1/155 (1%)	10/155 (6%)	22/155 (14%)
	PBO	66/159 (42%)	58/159 (36%)	8/159 (5%)	2/159 (1%)	0/159 (0%)	13/159 (8%)	19/159 (12%)
Trial 161	DA	59/175 (34%)	51/175 (29%)	24/175 (14%)	2/175 (1%)	3/175 (2%)	6/175 (3%)	10/175 (6%)
	PBO	59/169 (35%)	63/169 (37%)	17/169 (10%)	3/169 (2%)	3/169 (2%)	7/169 (4%)	4/169 (2%)
Trial 114	DA[a]	20/55 (36%)	15/55 (27%)	7/55 (13%)	2/55 (4%)	1/55 (2%)	0/55 (0%)	0/55 (0%)
	PBO	6/11 (55%)	6/11 (55%)	0/11 (0%)	0/11 (0%)	0/11 (0%)	0/11 (0%)	0/11 (0%)
Trial 291 (S1)	DA[a]	78/198 (39%)	58/198 (29%)	22/198 (11%)	1/198 (1%)	1/198 (1%)	8/198 (4%)	10/198 (5%)
	PBO	19/51 (37%)	18/51 (35%)	6/51 (12%)	0/51 (0%)	0/51 (0%)	0/51 (0%)	4/51 (8%)
Trial 291 (S2)	DA[a]	NR	37/125 (30%)	14/125 (11%)	NR	0/125 (0%)	6/125 (5%)	13/125 (10%)
	PBO	NR	7/31 (23%)	3/31 (10%)	NR	0/31 (0%)	2/31 (6%)	0/31 (0%)
Trial 232	DA	102/194 (53%)	84/194 (43%)	13/194 (7%)	3/194 (2%)	3/194 (2%)	11/194 (6%)	17/194 (9%)
	PBO	88/192 (46%)	77/192 (40%)	8/192 (4%)	1/192 (1%)	2/192 (1%)	8/192 (4%)	4/192 (10%)
Trial 145	DA	NR	138 (46%)	NR	NR	NR	NR	NR
	PBO	NR	121 (41%)	NR	NR	NR	NR	NR

[a] Darbepoetin alfa treatment groups combined.
DA = darbepoetin alfa; NR = not reported; PBO = placebo

Overview of adverse events in the supplementary trials

	Trial 231		Trial 156	
	DA 500µg Q3w	DA 2.25µg/kg Qw	DA 500µg Q3w + spFe	DA 500µg Q3w + ivFe
Subjects With at Least one On-study Adverse Event	312/353 (88%)	314/352 (89%)	160/193 (83%)	159/203 (78%)
Serious	138/353 (39%)	135/352 (38%)	65/193 (34%)	60/203 (30%)
Life-threatening	NR	NR	28/193 (15%)	23/203 (11%)
Severe, Life-threatening, or Fatal	157/353 (44%)	168/352 (48%)	NR	NR
Treatment Related Adverse Events	28/353 (8%)	28/352 (8%)	5/193 (3%)a	10/203 (5%)[a]
Serious	10/353 (3%)	10/352 (3%)	3/193 (2%)	4/203 (2%)
Life-threatening	NR	NR	0/193 (0%)	0/203 (0%)
Severe, Life-threatening, or Fatal	11/353 (3%)	11/352 (3%)	NR	NR
Study Discontinuations Due to Adverse Events	21/353 (6%)	22/352 (6%)	13/193 (6%)	9/203 (5%)
Fatal adverse events	38/353 (11%)	52/352 (15%)	15/193 (8%)	21/203 (10%)

[a] Related to darbepoetin alfa, not iv iron.
DA = darbepoetin alfa. NR = not reported; ivFe = intravenous iron; spFe = standard practice iron.

The extended assessment of comparative harms in relation to darbepoetin alfa was based on the Oncologic Drugs Advisory Committee (ODAC) background document. Rigorous combined analyses were performed to evaluate the safety of darbepoetin alfa, epoetin alfa, and other ESAs in the chemotherapy-induced anaemia (CIA) population. Studies of patient populations outside the registered CIA indication have caused concerns regarding tumour progression, survival, and cardiovascular/thromboembolic events. The PBS listing requested fits within the TGA approved use. However, the PBAC had some concerns that darbepoetin would be used in patients with cancers where the use of ESAs in another clinical context had an adverse effect on survival (e.g. head and neck cancer).

Pooled patient-level data analysis of darbepoetin alfa trials

Overall reported cardiovascular/thromboembolic (CV/TE) events occurred more frequently in the darbepoetin alfa group compared to the placebo group (HR 1.15; 95% CI: 0.86, 1.52); this result was likely to have been heavily influenced by the subcategory of TE events, which had a HR of 1.50 (95% CI: 0.97, 2.33). Hypertension was also reported at a higher frequency in the darbepoetin alfa group compared to the placebo group (HR 1.46; 95% CI: 0.78, 2.74). The HR for seizure was 1.43 (95% CI: 0.24, 8.58). None of these hazard ratios were statistically significant.

There have been recent publications raising concern about risk associated with ESAs in cancer, including a commentary in the NEJM that includes a summary of several studies using darbepoetin in which treatment was associated with shorter overall survival. However, these studies are in patient populations outside the registered CIA indication.

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

9. Clinical Claim

The submission claimed that darbepoetin alfa is significantly more effective than the main comparator (placebo/no pharmacological treatment) and has similar or less toxicity.

For PBAC's view of this claim, see Recommendation and Reasons.

10. Economic Analysis

The economic evaluation in the submission was based on results of a meta-analysis of the direct randomised trials. The re-submission presented two economic models. The first used treatment effects taken from the direct randomised trials, for the population with baseline Hb < 110g/L. The second used a further analysis carried out to determine the impact of applying the treatment effects to a subpopulation of patients with baseline Hb < 100g/L. Results of the trials at endpoint (12 weeks) were used in the economic analysis to provide effectiveness data at 16 weeks. The first model was termed the 'trial-based' evaluation and the second the 'modelled' evaluation.

Drug costs were derived from the supplementary trials using the proposed dosage regimen of darbepoetin alfa 500 μg per 3 weeks. Costs of delivery of blood transfusion, blood units, and thromboembolic events were modelled. Other costs related to the management of chemotherapy-induced anaemia were excluded. The PBAC considered that the submission overestimated the cost of transfusion.

A trial-based incremental cost/extra patient free of transfusion value in the range $15,000 to $45,000 was calculated in the submission.

A trial-based incremental cost/extra transfusion avoided value of <$15,000 was also calculated.

A base case modelled incremental cost/extra patient free of transfusion value in the range $15,000 to $45,000 was calculated in the submission.

A base case modelled incremental cost/extra transfusion avoided value of <$15,000 was calculated.

In the majority of sensitivity analyses, the cost per transfusion avoided remained < $15,000. These incremental cost effectiveness ratios were most sensitive to the clinical results for the transfusion incidence and could be in the range of $15,000 - $45,000 (for the population with Hb < 110 g/L) and $105,000 - $200,000 (for the subgroup with Hb < 100 g/L).

For further information on PBAC's view of these analyses, see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated to be in the range 10,000 – 50,000 in Year 5. The financial cost/year to the PBS was estimated to be in the range $60M - $100 M in Year 5.

The PBAC had significant uncertainty about the total cost to government and the estimates provided by the submission.

12. Recommendation and Reasons

The PBAC considered that there were a number of issues that would need to be addressed regarding the restriction and, in particular, the haemoglobin level at which therapy should commence which should be consistent with the NHMRC and the Australian and NZ guidelines for transfusion. Further, that 'at risk of requiring transfusion' and 'adequate iron stores' should be more clearly defined. In the latter case, the PBAC was concerned about possible use in patients with types of cancer where anaemia is known to occur due to blood loss (e.g. colorectal cancer). However, these issues were not considered to be a reason for rejection of the submission.

The PBAC noted the expert comment that there was insufficient evidence to conclude that erythropoeisis-stimulating agents (ESAs), such as darbepoetin caused increased harms or deaths in cancer patients due to stimulation of tumour growth, although there is an increased incidence of thromboembolic events. The PBAC noted the extended assessment of comparative harms in relation to darbepoetin alfa had been based on the Oncologic Drugs Advisory Committee (ODAC) background document in the submission. Rigorous combined analyses were performed to evaluate the safety of darbepoetin alfa, epoetin alfa, and other ESAs in the chemotherapy-induced anaemia (CIA) population. Studies of patient populations outside the registered CIA indication have caused concerns regarding tumour progression, survival, and cardiovascular/thromboembolic events. The PBS listing requested fits within the TGA approved use. However, the PBAC had some concerns that darbepoetin would be

used in patients with cancers where the use of erythropoeisis-stimulating agents in another clinical context had an adverse effect on survival (e.g. head and neck cancer).

The PBAC has previously considered changes in the need for transfusion and improvements in quality of life (QoL) and survival to be the patient-relevant outcomes for drugs that stimulate erythropoiesis. The PBAC noted that the trial data presented in the submission showed no statistically significant improvement in QoL or survival compared with blood transfusion, but show a statistically significant reduction in the proportion of patients requiring transfusion, and the number of units transfused per patient. In regard to safety, it was also noted that although there may be long term risks associated with blood transfusion, these may be of a lesser concern to patients, whose life expectancy is shortened due to their cancer, than improvement in quality of life.

While the clinical data clearly demonstrated that darbepoetin reduces chemotherapy-induced anaemia, the proportion of patients requiring any blood transfusion, and could reduce national demand for red blood cell units by a modest percentage, in the absence of a survival benefit or significant improvement in quality of life for patients, the base-case incremental cost-effectiveness ratios were considered unacceptably high.

The PBAC therefore rejected the submission because of uncertain cost-effectiveness.

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

Although disagreeing with the recommendation, the Sponsor intends to work collaboratively with the PBAC to find a way to move forward with reimbursement of darbepoetin alfa for the treatment of chemotherapy induced anaemia.