

7.04 DARBEPOETIN ALFA,

**Injection 200 micrograms in 0.4 mL pre-filled syringe,
Injection 300 micrograms in 0.6 mL pre-filled syringe,
Injection 500 micrograms in 1.0 mL pre-filled syringe,
Aranesp[®], Amgen Australian Pty Ltd.**

1 Purpose of Application

- 1.1 The resubmission requested a Section 100 (Highly Specialised Drugs Program), Authority Required listing for darbepoetin alfa for treatment of moderate to severe chemotherapy induced anaemia (CIA). The PBAC has previously reviewed darbepoetin alfa for CIA in June 2003, November 2007 and March 2008 (minor submission). Previous submissions were rejected on the basis of uncertain cost-effectiveness, concerns were also expressed by the PBAC over the wording of the restrictions, quality of life (QoL) improvements, and safety events occurring in patient populations outside the registered CIA indication.
- 1.2 The requested basis for listing was cost-effectiveness compared to standard medical management (placebo or no pharmacological treatment), which includes blood transfusions where clinically indicated.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Patients with chemotherapy induced anaemia (CIA)
Intervention	Darbepoetin alfa (rch) (Aranesp®)
Comparator	Standard medical management (placebo or no pharmacological treatment), includes blood transfusions where clinically indicated.
Outcomes	A range of outcomes including: <ul style="list-style-type: none"> • Overall survival and PFS. • Transfusion outcomes: transfusion incidence. • Haematological outcomes: Hb response (≥ 20 g/L over baseline), change in Hb. • Patient reported outcomes: FACT-fatigue scale. • Safety: adverse events, thromboembolic events and mortality.
Clinical claims	In patients with CIA, darbepoetin alfa is more effective than standard medical management at improving Hb response rates and reducing RBC transfusions. Darbepoetin alfa is non-inferior in terms of overall survival and PFS compared to standard medical management and has non-inferior safety.

Abbreviations: Hb=haemoglobin; FACT = Functional Assessment of Cancer Therapy; PFS=progression-free survival
Source: Table 1.1, p14 of the resubmission.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
DARBEPOETIN ALFA					
Injection 200 micrograms in 0.4mL pre-filled syringe,	1	1	2	\$ [redacted] (Public)	Aranesp®, Amgen
Injection 300 micrograms in 0.6mL pre-filled syringe,				\$ [redacted] (Private)	Aust Pty Ltd
				\$ [redacted] (Public)	
				\$ [redacted] (Private)	
Injection 500 micrograms in 1.0mL pre-filled syringe				\$ [redacted] (Public)	
				\$ [redacted] (Private)	

Category/Program	Section 100 – Highly Specialised Drugs Program (<i>Private and Public Hospitals</i>)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	Acute
Severity:	Moderate to severe
Condition:	Chemotherapy-induced anaemia
PBS Indication:	Acute moderate to severe chemotherapy-induced anaemia
Treatment phase:	Initial
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Patient must not receive more than three cycles of treatment under this restriction (9 weeks)
Clinical criteria:	Patient must be receiving myelosuppressive chemotherapy. AND Patient must have a non-myeloid malignancy AND Patient must have a haemoglobin level of less than 100 g per L,

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	AND Patient must not receive more than 9 weeks of darbepoetin alfa per course of chemotherapy treatment under this restriction.
Prescriber Instructions	Treatment is by fixed dose of either 500 mcg (starting dose), 300 mcg or 200 mcg every 3 weeks. 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.

Name, Restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
DARBEPOETIN ALFA Injection 200 micrograms in 0.4mL pre-filled syringe,	1	1	5	\$ [REDACTED] (Public) \$ [REDACTED] (Private)	Aranesp®, Amgen Aust Pty Ltd
Injection 300 micrograms in 0.6mL pre-filled syringe,				\$ [REDACTED] (Public)	
Injection 500 micrograms in 1.0mL pre-filled syringe				\$ [REDACTED] (Public) \$ [REDACTED] (Private)	

Category/Program	Section 100 – Highly Specialised Drugs Program (<i>Private and Public Hospitals</i>)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	Acute
Severity:	Moderate to severe
Condition:	Chemotherapy-induced anaemia
PBS Indication:	Acute moderate to severe chemotherapy-induced anaemia
Treatment phase:	Continuing
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Patient may receive treatment for a maximum of one cycle (dose) of darbepoetin alfa following completion of chemotherapy or until the target Hb of 120 g per L is reached
Clinical criteria:	Patient must be have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must have responded to treatment with darbepoetin alfa, AND Patient must not receive more than one cycle (dose) of darbepoetin alfa following completion of a course of chemotherapy.
Prescriber Instructions	Response to treatment is defined as a 20 g per L increase in Hb while receiving treatment with darbepoetin alfa. Treatment is by fixed dose of either 500 mcg (starting dose), 300 mcg or 200 mcg every 3 weeks 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.

2.2 Compared to the November 2007 resubmission, the proposed restriction in this resubmission is simpler. While the resubmission improved aspects of the restriction wording compared to November 2007, the proposed restriction in this resubmission removed the specification of the maximum number of doses of darbepoetin alfa permitted per course of chemotherapy:

- Without this criterion, the requested restrictive wording is considered ambiguous in relation to the maximum duration of therapy of darbepoetin alfa accompanying the current chemotherapy course, as technically, patients can keep getting prescriptions of 1 plus 5 repeats for darbepoetin alfa under continuing therapy. This manner of use if observed would not be consistent with assumptions used by the resubmission in both the modelled economic evaluation and the financial estimates where patients are assumed to be treated for up to a maximum of 21 weeks (18 weeks in conjunction with chemotherapy and one additional dose post chemotherapy, up to a maximum of 7 doses).
- The omission of a clear statement on maximum allowable doses of darbepoetin alfa per chemotherapy course also means there is no clear guidance in the requested restrictions for patients who may require darbepoetin alfa with a further course of chemotherapy in the future. Based on the requested restriction wording, if a patient has previously responded to darbepoetin alfa, then the patient potentially can reinstate darbepoetin alfa on continuation therapy (i.e., without having to redemonstrate efficacy). If a patient has previously failed, then they may retriial darbepoetin alfa and continue therapy if they are able to meet the continuation criteria this time. Efficacy of darbepoetin alfa in patients who have previously failed therapy is unclear.

2.3 While there are several approved dosing regimens for darbepoetin alfa in CIA, including weight based dosing of differing frequencies, the resubmission is only requesting PBS listing for the fixed dosing regimen of darbepoetin alfa 500 mcg once every 3 weeks (Q3W). The requested darbepoetin alfa 300 mcg and 200 mcg strengths preparations are intended for dose reduction only when patients' haemoglobin (Hb) levels approach the upper target of 120g/L.

2.4 The proposed use of darbepoetin alfa on PBS is generally consistent with international guidelines (European Society of for Medical Oncology (ESMO, 2018¹), the National Comprehensive Cancer Network in the US (NCCN, 2018²) and joint guidelines of the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) in 2010 and NICE Guidance TA323 (Erythropoiesis-stimulating agents (ESAs) for CIA) (NICE, 2014³). ESAs are not recommended for patients with cancer who are not receiving chemotherapy or who are receiving radiotherapy without chemotherapy (with the exception of patients with low risk myelodysplastic syndrome (MDS), because ESAs have been associated with an increased risk of death in such patients. The pre-PBAC response noted that the FDA released the Risk Evaluation and

¹ Aapro, M., Beguin, Y., Bokemeyer, C. & Dicato, M., 2018. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. *Annals of Oncology*, pp. 1-15.

² NCCN, 2018. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology – Cancer and Chemotherapy-Induced Anemia. Version 3.

³ NICE, 2014. Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (TA323).

Mitigation Strategy requirements in 2017, satisfied that risks can be communicated by the current product prescribing information. The pre-PBAC response argued that the FDA considered that the appropriate use of ESAs is supported by the joint ASH and ASCO clinical guidelines which provide a basis for the standard of care in clinical oncology.

- 2.5 The ESC noted that one aspect, inconsistent between the guidelines was that the NCCN 2018 guidelines do not recommend ESA for patients receiving myelosuppressive chemotherapy with curative intent (examples of cancers of which there is a curative intent include: early stage breast cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, testicular cancer, early stage non-small cell lung cancer, small cell lung cancer etc.). The European Medicines Agency (EMA) recommended that blood transfusions are preferred over ESAs in cancer patients who have chemotherapy-related anaemia and a "reasonably long life expectancy" (EMA 2008⁴). Review of the same data also led the FDA to mandate a label change for ESAs, stating that their use was not indicated in patients receiving myelosuppressive chemotherapy when the anticipated outcome was cure, regardless of the specific type of malignancy (FDA Aranesp[®] prescribing information). However, updated guidelines for the use of ESAs from ASH/ASCO (2010) and the NICE guidance on ESAs in CIA (2014) do not differentiate between patients receiving potentially curative cancer therapy and those undergoing palliative cancer treatment. The Therapeutic Goods Administration (TGA) has not placed any restrictions to limit darbepoetin alfa use based on a patient's predicted survival. The Pre-Sub-Committee Response (PSCR) argued that the totality of the NCCN and EMA recommendations was not represented by the above statements and presented those for use in patients with Hb < 100 g/L. The ESC noted that the recommendations for use in patients with Hb < 100 g/L were not in dispute. The ESC noted that to date no study or meta-analysis had investigated the outcomes of ESA therapy according to chemotherapy aim or intent.
- 2.6 The ESC noted that both the NCCN 2018 guidelines and the FDA do not recommend ESA as a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anaemia.
- 2.7 International guidelines also recommend use of ESAs for MDS, a group of diseases that affect the production of normal blood cells in the bone marrow (ASH/ASCO 2010 and NCCN, 2018). While current clinical trial evidence, professional society guidelines, and TGA approval indications do NOT support the use of ESAs for the treatment of anaemia due to malignancy in the absence of chemotherapy, use of ESAs in patients with lower-risk MDS to avoid transfusions is an exception to this recommendation, particularly for patients with low to intermediate-1 risk MDS. Given MDS is often considered a precursor to myeloid cancers (and thus may satisfy PBS requirement for

⁴ EMA Press release 26 June 2008, available at <https://www.ema.europa.eu/en/news/emea-recommends-new-warning-epoetins-their-use-cancer-patients> (Accessed on November 02, 2010)

non-myeloid malignancy), if darbepoetin is listed on the PBS for CIA as proposed, there may be leakage of use to this population.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 Darbepoetin alfa was TGA registered on 13 November 2002 for “treatment of anaemia and reduction of transfusion requirements in patients with non-myeloid malignancies where anaemia develops as a result of concomitantly administered chemotherapy”.
- 3.2 Darbepoetin alfa is also registered (and currently PBS funded) for use in anaemia associated with chronic renal failure.

Previous PBAC consideration

- 3.3 Table 2 summarises key outstanding matters from the previous major PBAC considerations in November 2007 and how the resubmission addressed those concerns.

Table 2: Summary of outstanding matters of concern

Component	Matters of concern	How the resubmission addresses them
PBS restriction	The Hb level at which therapy should be commenced should be consistent with the NHMRC and the Australian and NZ guidelines for transfusion (darbepoetin alfa November 2007 PSD; first paragraph of 12. Recommendation and Reasons)	Australian guidelines on blood management (NHMRC 2001; Australian Patient Blood Management Guidelines) recommend RBC transfusions for patients with Hb levels < 70 g/L or if Hb is in the range 70-100 g/L transfusions are recommended if there is need to relieve clinical signs and symptoms and prevent significant morbidity and mortality. Based on these, the proposed Hb based criteria for transfusions of Hb < 100 g/L in this resubmission appeared to be reasonable.
	'At risk of requiring transfusion' and 'adequate iron stores' should be more clearly defined (darbepoetin alfa November 2007 PSD; first paragraph of 12. Recommendation and Reasons)	These criteria have been appropriately excluded in this resubmission.
Outcomes	The PBAC has previously considered changes in the need for transfusion and improvements in QoL and survival to be the patient-relevant outcomes for drugs that stimulate erythropoiesis (darbepoetin alfa November 2007 PSD; third paragraph of 12. Recommendation and Reasons).	The resubmission reported results of additional trials assessing Hb and QoL (fatigue) outcomes, including FACT-Fatigue subscale scores.
Safety	The PBAC noted the expert comment that there was insufficient evidence to conclude that ESAs such as darbepoetin caused increased harms or deaths in cancer patients due to stimulation of tumour growth, although there is an increased risk of thromboembolic events (darbepoetin alfa November 2007 PSD; second paragraph of 12. Recommendation and Reasons).	The resubmission included the recently completed Study 782 as key clinical evidence on overall survival and progression-free survival.
PBAC decision	In the absence of a survival benefit or a significant improvement in QoL for patients, the base case incremental cost-effectiveness ratios were considered unacceptably high (darbepoetin alfa November 2007 PSD; last paragraph of 12. Recommendation and Reasons).	Trial data presented in the resubmission do not show a significant benefit in survival or QoL for darbepoetin alfa. The results of the economic model are driven by costs of transfusions avoided and QoL benefits assumed with improvements in Hb levels.

Abbreviations: ESAs=erythropoiesis-stimulating agents; FACT = Functional Assessment of Cancer Therapy; = Hb = haemoglobin; QoL = quality of life; RBC = Red blood cells

Source: Table 1.6, pp.22-24 of the resubmission.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Anaemia is defined as a Hb concentration of less than 120 g/L in women and less than 130 g/L in men (Table 1.2, p17 of resubmission). Moderate anaemia is defined as Hb < 100 g/L and ≥ 80 g/L, and severe anaemia is defined as Hb < 80 g/L. Myelosuppressive chemotherapeutic agents induce anaemia by directly impairing haematopoiesis in bone marrow. In addition to bone marrow damage, platinum-containing drugs damage kidney cells that produce erythropoietin. Fatigue is common in oncology patients undergoing anti-cancer treatment and is a disabling symptom affecting daily life activities and QoL (Groopman and Itri 1999).
- 4.2 Darbepoetin alfa (rch) is an erythropoiesis stimulating protein that is used to treat anaemia caused by kidney disease or cancer treatments. The ESC noted that, unlike a RBC transfusion which quickly increases Hb level, darbepoetin alfa gradually increases the Hb concentration over a period of weeks. The ESC noted that there are potential harms (e.g. serious infections, immune mediated adverse reactions) associated with RBC transfusions. However, the ESC considered that the delay in treatment response compared to a RBC transfusion would likely limit the use of darbepoetin alfa in clinical practice.
- 4.3 Darbepoetin alfa is proposed to be given in addition to standard management, where standard management includes RBC transfusions (for severe anaemia), iron supplementation, vitamin B12 or folate as necessary. In clinical trials, the main effect of darbepoetin alfa was to reduce the proportion of patients needing RBC transfusions. The main co-administered therapy is chemotherapy; the resubmission argued that no differences in chemotherapy usage would be expected due to the availability of darbepoetin alfa. This may not be entirely appropriate given CIA may result in dose delay or dose reduction in chemotherapy cycles, differences in chemotherapy dose or timing of administration were not considered in the resubmission's modelled economic evaluation.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The resubmission nominated no pharmacological treatment or standard medical management as the main comparator, on the justification that there are no drug therapies currently listed on the PBS for the treatment of CIA. The main effect of darbepoetin alfa is to reduce RBC transfusions, and hence RBC units are replaced by darbepoetin alfa in practice. The ESC noted that the comparator of standard medical management was previously accepted by the PBAC in its November 2007 consideration. The PBAC considered that the comparator was appropriate.
- 5.2 Three other ESAs: epoetin alfa, epoetin beta and epoetin lambda are registered for the treatment of CIA. Similar to darbepoetin they are only currently PBS-listed for use in chronic renal failure. The resubmission did not consider these agents to be near market or potential future comparators on the basis that darbepoetin alfa is the only registered agent with a dose every three weeks. It was noted that the PBAC had

previously considered a submission for epoetin alfa (Eprex®) at its June 2000 PBAC meeting, but rejected the application due to lack of data supporting a claim of superiority in terms of reduced transfusion requirements, improved QoL and survival. In the UK, ESAs (epoetin alfa, epoetin beta, and darbepoetin alfa) are recommended, within their marketing authorisations, for treating anaemia in people with cancer who are having chemotherapy (NICE Guidance, November 2014).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The resubmission was based on 11 randomised controlled trials (RCTs), including:

- One main, recent, safety RCT comparing darbepoetin alfa 500 mcg fixed dose regimen Q3W to placebo: Study 782 (N=2,549);
- Eight RCTs (main efficacy trials) for darbepoetin alfa versus placebo, which include other darbepoetin alfa registered dosing regimens: Study 297 (N=320); Study 161 (N=349); Study 114 (N=66); Study 291(S1) (N=259); Study 232 (N=391); Study 145 (N=600); Katsumata 2009 (N=207) and Suzuki 2008 (N=123); and
- Two supplementary non-placebo-controlled trials also using the fixed dose darbepoetin alfa regimen of 500 mcg Q3W: Study 231 (N=705) and Study 156 (N=398).

6.4 The resubmission also included two published meta-analyses examining the efficacy and safety of darbepoetin alfa in the sub-group of patients with a baseline Hb level ≤ 100 g/L (Boccia 2016 and Pirker 2016). Both of these meta-analyses examined data from Studies 297, 232, and 145; Pirker 2016 also included Study 161. Efficacy outcomes included Hb response and RBC transfusions.

6.5 Most of the included evidence has previously been considered by the PBAC. The only new evidence presented in this resubmission was Study 782, Katsumata 2009 (abstract only) and Suzuki 2008 (abstract only), with limited results available for Katsumata 2009 and Suzuki 2008. Study 782 is a recent safety RCT, with overall survival and progression-free survival (PFS) as its main outcomes.

6.6 Details of the trials and meta-analyses presented in the resubmission are summarised in Table 3.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Main safety and dosage regimen trial		
Study 782	A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term Safety and Efficacy of Darbepoetin Alfa Administered at 500 µg Once-Every-3-Weeks in Anemic Subjects With Advanced Stage Non-small Cell Lung Cancer Receiving Multi-cycle Chemotherapy.	June 2018
	Gascon P et al. Long-term safety and efficacy of darbepoetin alfa in subjects with advanced stage NSCLC receiving multi-cycle chemotherapy	<i>Journal of Thoracic Oncology</i> . 2016; 11 (10S): S214-215.
	Gascon P et al. Randomized phase 3 trial of the long-term safety of darbepoetin alfa in patients with non-small cell lung cancer (NSCLC) with chemotherapy-induced anemia (CIA).	<i>Journal of Thoracic Oncology</i> . 2014; 9 (4 Suppl. 1): S48-S49. Conference: 17 th World Conference of the International Association for the Study of Lung Cancer, IASLC 2016. Austria.
	Gage J et al. Long-term safety and efficacy of darbepoetin alfa in subjects with advanced stage NSCLC receiving multi-cycle chemotherapy	<i>Journal of Thoracic Oncology</i> . 2017; 12(1): S1091-S1092.
	Henry D et al. Randomized, double-blind, placebo-controlled, phase 3 noninferiority study of darbepoetin alfa for anemia in patients with advanced NSCLC: An ad hoc subgroup analysis of patients with baseline hemoglobin ≤ 10.0 g/dL.	ESMO. 2018 Congress. Poster 4579. <i>Annals of Oncology</i> 2018; 29 (suppl.8).
Main efficacy trials		
Study 297	A Double-blind, Placebo-controlled, Randomised Study of Novel Erythropoiesis Stimulating Protein (NESP) for the Treatment of Anaemia in Lung Cancer Subjects Receiving Multicycle Platinum-containing Chemotherapy.	June 2001.
	Vansteenkiste J et al. Double-blind, placebo-controlled, randomised Phase 3 trial of darbepoetin alfa in lung cancer patients receiving chemotherapy.	<i>J Natl Cancer Inst</i> . 2002; 94(16): 1211-1220.
Study 161	A Multicenter, Blinded, Placebo-controlled, Randomised Study of Novel Erythropoiesis Stimulating Protein (NESP) for the Treatment of Anaemia in Subjects with Lymphoproliferative Malignancies Receiving Chemotherapy.	August 2002.
	Hedenus M et al. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomised, double-blind, placebo-controlled study.	<i>British Journal of Haematology</i> . 2003; 122: 394-403.
Study 114	A Multi-centre, Blinded, Placebo-controlled, Randomised, Dose-finding Study of Novel Erythropoiesis Stimulating Protein Administered by Subcutaneous Injection for the Treatment of Anaemia in Subjects With Lymphoproliferative Malignancies Receiving Chemotherapy.	March 2001,
	Hedenus M et al. Randomised, dose-finding study of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies.	<i>British Journal of Haematology</i> . 2002; 119:79-86.

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Trial ID	Protocol title/ Publication title	Publication citation
Study 291 (S1)	A Randomised, Double-blind, Placebo-controlled, Dose-finding Study of Novel Erythropoiesis Stimulating Protein (NESP) Administered Once Every Three Weeks by Subcutaneous (SC) Injection for the Treatment of Anaemia in Subjects with Solid Tumours Receiving Multicycle Chemotherapy. Kotasek D et al. Darbepoetin alfa administered every 3 weeks alleviates anaemia in patients with solid tumours receiving chemotherapy; results of a double-blind, placebo-controlled, randomised study.	June 2002. <i>European Journal of Cancer</i> . 2003; 39: 2026-2034.
Study 232	A Randomised, Double-blind, Placebo-controlled Study of darbepoetin alfa for the Treatment of Anaemia in Subjects with Non-myeloid Malignancy Receiving Multicycle Chemotherapy. Hernandez E et al. Randomized, double-blind, placebo-controlled trial of every-3-week darbepoetin alfa 300 micrograms for treatment of chemotherapy-induced anemia.	December 2005. <i>Current Medl Resh & Opinions</i> . 2009; 25 (9): 2109-2120.
Study 145	A Phase 3 Randomised, Double-blind, Placebo-controlled Study of Patients with Previously Untreated Extensive-Stage Small Cell Lung Cancer (SCLC) Treated with Platinum Plus Etoposide Chemotherapy With or Without Darbepoetin alfa. Pirker R et al. Safety and efficacy of darbepoetin alfa in previously untreated extensive-stage small-cell lung cancer treated with platinum plus etoposide.	August 2007. <i>Journal of Clin Oncol</i> . 2008; 26(14): 2342-2349.
Katsumata 2009	Katsumata N et al. Randomized, double-blind, placebo-controlled phase III study of weekly administration of darbepoetin alfa in anemic patients with lung or gynecologic cancer receiving platinum-containing chemotherapy.	4A-S20-03. <i>Vox Sanguinis</i> , 2009. p. 58
Suzuki 2008	Suzuki Y et al. Randomized, placebo-controlled phase II study of darbepoetin alfa (DA) administered every three weeks (Q3W) in patients with chemotherapy-induced anemia (CIA).	<i>Ann Oncol</i> . 2008; 19(Suppl8); viii277.
Supplementary trials		
Study 231	A randomised, Double-blind, Active-controlled, Study of Darbepoetin alfa for the Treatment of Anaemia in Subjects with non-myeloid Malignancy Receiving Multicycle Chemotherapy. Canon J-L et al. Randomised, double-blind, active-controlled trial of every-3-week darbepoetin alfa for the treatment of chemotherapy-induced anaemia,	April 2005 <i>Journal of the National Cancer Institute</i> . 2006; 98: 273-84.
Study 156	A Randomised Open-Label Study Of Darbepoetin alfa Administered Every Three Weeks With Or Without Parenteral Iron In Anaemic Subjects With Non-Myeloid Malignancies Receiving Chemotherapy. Bastit L et al. Randomized, multicentre, controlled trial comparing the efficacy and safety of darbepoetin alfa administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia.	February 2007 <i>Journal of Clin Oncology</i> . 2008; 26(10): 1611-1618.
Supplementary meta-analyses		
Boccia 2016	Boccia RV, Henry DH, Belton L et al. Efficacy and safety of darbepoetin alfa initiated at haemoglobin \leq 10 g/dL in patients with stage IV cancer and chemotherapy-induced anemia	<i>Cancer Med</i> . 2016; 5(12): 3445-3453.
Pirker 2016	Pirker R, Hedenus M, Vansteenkiste J et al. Effectiveness of darbepoetin alfa for chemotherapy-induced anemia when initiated at haemoglobin \leq 10 g/dL	<i>Clin Therapeutics</i> . 2016; 38(1): 122-135.

Source: Tables 2.4-2.6, pp. 46-49 of the resubmission.

6.7 The key features of the randomised trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Intervention	Outcome(s)	Use in modelled evaluation
Main safety and dosage regimen trial: darbepoetin alfa 500 mcg Q3W v placebo							
Study 782	2549	R, DB, MC, PC, a	Low	Lung cancer patients receiving chemotherapy; Hb \leq 110 g/L	Darbepoetin alfa 500 mcg Q3W (to a Hb ceiling of 120 g/L) vs Placebo.	Primary: OS Secondary: PFS; RBC transfusions	Not used
Main efficacy trials							
Study 297	320	R, DB, MC, PC, 12 wks	Low	Lung cancer patients receiving chemotherapy; Hb \leq 110 g/L	Darbepoetin alfa 2.25 mcg/kg once every week (QW) vs Placebo.	Primary: RBC transfusions Secondary: Hb response; FACT-F score Long-term follow-up: Time to disease progression, time to death	Not used
Study 161	349	R, DB, MC, PC, 12 wks	Low	LPM patients receiving chemotherapy; Hb \leq 110g/L	Darbepoetin alfa 2.25 mcg/kg QW vs Placebo.	Primary: Hb response Secondary: RBC transfusions; FACT-F score Long-term follow-up: Time to disease progression, time to death	Not used
Study 114	66	R, DB, MC, PC, 12 wks	Low	LPM patients receiving chemotherapy; Hb \leq 110g/L	Darbepoetin alfa 2.25 mcg/kg QW ^b vs Placebo.	Primary: Time to sustained Hb response; Secondary: RBC transfusions; Hb response	Not used
Study 291 (S1)	259	R, DB, MC, PC, 12 wks	Low	Solid tumour patients receiving chemotherapy; Hb \leq 110 g/L	Darbepoetin alfa 6.75 mcg/kg Q3W ^c vs Placebo.	Primary: Safety Secondary: RBC transfusions; Hb response	Not used
Study 232	391	R, DB, MC, PC, 15 wks	Low	NMM patients receiving chemotherapy; Hb \leq 110 g/L	Darbepoetin alfa 300 mcg Q3W (dose escalation criteria ^d) vs Placebo.	Primary: RBC transfusions Secondary: FACT-F score; EQ-5D	Not used
Study 145	600	R, DB, MC, PC, e	Low	Lung cancer patients receiving chemotherapy ; Hb \geq 90 and \leq 130 g/L	Darbepoetin alfa 300 mcg once weekly for first 4 weeks, followed by 300 mcg Q3W for remainder of treatment period (dose escalation criteria ^f) vs Placebo	Primary: Change in Hb level, survival Secondary: FACT-F score Long-term follow-up: overall survival	Not used
Katsumata 2009	207	R, DB, MC, PC, 12 wks	Low	Lung or gynecologic cancer patients receiving chemotherapy; Hb \leq 110 g/L; Japanese	Darbepoetin alfa 2.25 mcg/kg once every week vs Placebo.	Primary: transfusion trigger (Hb \leq 80 g/L or RBC transfusion) Secondary: RBC transfusions	Not used

Trial	N	Design/ duration	Risk of bias	Patient population	Intervention	Outcome(s)	Use in modelled evaluation
Suzuki 2008	123	R, MC, PC, 12 wks	Unclear	NMM patients receiving chemotherapy; Hb ≤ 100 g/L; Japanese	Darbepoetin alfa 4.5 or 6.75 mcg/kg Q3W vs Placebo. Hb held < 120 g/L at any dosing visit.	Primary: Hb response Secondary: RBC transfusions; FACT-An score	Not used
Supplementary trials							
Study 231	705	R, DB, PG, MC, dose finding study, 15 wks	Low	NMM patients receiving chemotherapy; Hb ≤ 110 g/L	Darbepoetin alfa 500 mcg Q3W vs darbepoetin alfa 2.25 mcg/kg QW	Primary: RBC transfusion Secondary: Hb response ^g , FACT-F score, EQ-5D	Hb response ^g
Study 156	398	R, OL, PG, MC 16 wks	High	NMM patients receiving chemotherapy; Hb ≤ 110 g/L	Darbepoetin alfa 500 mcg Q3W with IV iron vs oral iron	Primary: Hematopoietic response Secondary: RBC transfusions; Hb response ^g , FACT-F score	Not used

Abbreviations: DB=double blind; MC=multicentre; OL=open label; PC=placebo controlled; PG=parallel group; R=randomised; N=number randomised; FACT-AN=Functional Assessment of Cancer Therapy – Anemia; FACT-F=Functional Assessment of Cancer Therapy - Fatigue; Hb=haemoglobin; IV=intravenous; LPM= lymphoproliferative malignancy; NMM=non-myeloid malignancy; OS=overall survival; PFS=progression-free survival; RBC = red blood cell.

^a Study 782: Duration of treatment was until 3 weeks after the completion of chemotherapy or upon determination of disease progression, whichever occurred first.

^b Study 114: Doses ranged from 1.0 to 4.5 mcg/kg once weekly, with only the 2.25 mcg/kg once weekly dose being a registered regimen.

^c Study 291(S1): Doses ranged from 4.5 to 15.0 mcg/kg Q3W, with only the 6.75 mcg/kg Q3W dose being a registered regimen.

^d Study 232: Dose escalation criteria (i) Week 4: If Hb < 90g/L, dose increased to 500 mcg Q3W; and (ii) Week 7: If Hb < 100g/L and increase < 10g/L, dose increased to 500 mcg Q3W.

^e Study 145: Duration of treatment was throughout 6 cycles of chemotherapy and for 3 weeks after the last dose of on-study chemotherapy.

^f Study 145: Dose escalation criteria: if Hb < 110g/L during study weeks where no dose was planned, an additional weekly dose was to be administered:

^g Studies 231 and 156: Hb response was not a prospectively defined outcome in Study 231 and Study 156. Results for this endpoint were generated for the November 2007 resubmission to allow a comparison with the other trials.

Source: compiled during the evaluation from submitted trial and published reports.

6.8 The ESC noted that none of the outcomes from the main Study 782 or the main efficacy trials were used in the modelled economic evaluation. Hb response from the darbepoetin alfa fixed dose arm of Study 231 was used as the main evidence to populate the modelled economic evaluation. The ESC considered the resubmission's justification for selecting Study 231 was flawed (see further discussion below). It was also noted that Hb response was not a prospectively defined outcome in this trial.

Comparative effectiveness

6.9 The resubmission's clinical claims were based on haemoglobin outcomes, transfusion outcomes, overall survival, PFS, patient reported outcomes (including QoL) and safety. The resubmission provided data from three new studies (Study 782, Katsumata 2009 and Suzuki 2008). Overall survival was the primary outcome in Study 782. Data from the other trials were unchanged.

6.10 The PBAC previously considered changes in the need for transfusion, and improvements in QoL and survival to be the patient-relevant outcomes (November 2007 resubmission). In Study 782, non-inferiority was declared if the upper

confidence limit for the hazard ratio for darbepoetin alfa versus placebo was < 1.15 (using a one-sided significance level of 0.025), for the outcome of overall survival. If non-inferiority was declared for overall survival, non-inferiority was declared for PFS if it met the same non-inferiority margin that applied to overall survival.

- 6.11 Tables 5 and 6 summarise the outcomes of median time to death and median time to disease progression or death, respectively, in the included trials, which reported these outcomes (i.e. Study 782, Study 297, Study 161 and Study 145). Studies 782, 297 and 145 were all conducted in lung cancer patients, whereas Study 161 enrolled patients with lymphoproliferative malignancies.

Table 5: Results of median time to death in months (95% CI) in Studies 782, 297, 161 and 145

Trial ID	Darbepoetin alfa	Placebo	Hazard ratio for time to death (95% CI) ^a
All patients			
Study 782	9.46 (8.90, 10.12) months	9.26 (8.25, 10.02) months	HR=0.92 (95% CI: 0.83, 1.01) ^a
Study 297	10.62 months	7.85 months	HR=0.77 (95% CI: 0.59, 1.01) ^b
Study 161	30.23 months	41.77 months	HR=1.36 (95% CI: 1.02, 1.82) ^c
Study 145	9.23 months	9.23 months	HR=0.93 (95% CI: 0.78, 1.10) ^d
Sub-group* – screening Hb < 100 g/L			
Study 782	9.03 months	9.07 months	HR=0.95 (95% CI: 0.83, 1.08) ^e
Sub-group* – screening Hb ≥ 100 g/L			
Study 782	9.99 months	9.46 months	HR=0.87 (95% CI: 0.76, 1.00) ^e

Grey shading indicate data previously seen by the PBAC.

Abbreviations: Hb = haemoglobin; CI = confidence interval; n = number of participants with event; N = total participants in group.

^a note HR < 1 indicates lower risk of death for darbepoetin alfa versus placebo, HR>1 indicates a higher risk of death for darbepoetin alfa versus placebo.

* Pre-specified subgroup analyses reported in CSR of Study 782

^a Study 782: Based on Cox-proportional hazards model; stratification factors were geographic region, histology, screening Hb.

^b Study 297: Based on Cox-proportional hazards model, adjusting for treatment group, tumor type and region.

^c Study 161: Based on Cox-proportional hazards model adjusting for the effects of malignancy type, chemotherapy before randomisation, and region. Updated for final follow-up assessment (4th April 2005).

^d Study 145: Based on stratified Cox regression model using baseline ECOG category and baseline lactate dehydrogenase category as stratification factors.

^e Study 782: Hazard ratio with 95% CI was generated from an unstratified Cox regression for each level of a given stratification factor.

Source: Tables 2.35, 2.67, Figure 2.10; Figure 2.12; pp.118-137 of the resubmission.

Table 6: Results of median time to disease progression (and/or death) in months in Studies 782, 297, 161 and 145

Trial ID	Darbepoetin alfa	Placebo	Hazard ratio (95% CI)
A) Median time to disease progression in months (95% CI)			
Study 297	6 months (26 weeks)	4.62 months (20 weeks)	HR=0.79 (95% CI: 0.61, 1.01) ^b
B) Median time to disease progression or death in months (95% CI)			
All patients			
Study 782	4.80 months (4.37, 5.32)	4.34 months (4.17, 4.70)	HR=0.95 (95% CI: 0.87, 1.04) ^a
Study 297	5.31 months (23 weeks)	4.62 months (20 weeks)	HR=0.80 (95% CI: 0.63, 1.02) ^b
Study 161	14.31 months (62 weeks)	16.15 months (70 weeks)	HR=1.01 (95% CI: 0.79, 1.29) ^c
Study 145	5.54 months (24 weeks)	5.54 months (24 weeks)	HR=1.02 (95%CI: 0.86, 1.21) ^d
Sub-group – screening Hb < 100 g/L			
Study 782	4.34 months (19 weeks)	4.17 months (18 weeks)	HR=0.94 (95% CI: 0.83, 1.06) ^e
Sub-group – screening Hb ≥ 100 g/L			
Study 782	5.42 months (23 weeks)	4.53 months (20 weeks)	HR=0.96 (95% CI: 0.85, 1.10) ^e

Grey shading indicate data previously seen by the PBAC.

Abbreviations: Hb = haemoglobin; CI = confidence interval; n = number of participants with event; N = total participants in group

[^] note HR<1 indicates lower risk of disease progression (and/or death) for darbepoetin alfa versus placebo, HR>1 indicates a higher risk of disease progression (and/or death) for darbepoetin alfa versus placebo.

^a Study 782: Based on Cox-proportional hazards model; stratification factors were geographic region, histology, screening Hb.

^b Study 297: Based on Cox-proportional hazards model, adjusting for treatment group, tumor type and region.

^c Study 161: Based on Cox-proportional hazards model adjusting for the effects of malignancy type, chemotherapy before randomisation, and region

^d Study 145: Based on Cox-proportional hazards regression model with treatment as a factor, stratified by baseline ECOG and baseline LDH.

^e Study 782: Hazard ratio with 95% CI was generated from an unstratified Cox regression for each level of a given stratification factor.

Source: Tables 2.36, 2.68, pp.120-137 of the resubmission.

6.12 In Studies 782, 297 and 145, the median times to death were similar in patients treated with darbepoetin alfa and placebo. In Study 161, the risk of death was significantly higher in patients randomised to darbepoetin alfa therapy versus placebo (HR for death darbepoetin alfa versus placebo: 1.36: 95% CI: 1.02, 1.82). Cox proportional hazards modelling revealed that previous chemotherapy (categorised as heavily pre-treated and not-heavily pre-treated) had a statistically significant effect on time to death. Further analysis of the strata defined by malignancy type and previous chemotherapy indicated that the increased risk in subjects receiving darbepoetin alfa was limited to the heavily pre-treated strata (i.e., subjects who received ≥ 2 previous lines of chemotherapy or 1 line of chemotherapy and a stem-cell transplant). Because of the small number of subjects in the heavily pre-treated myeloma and lymphoma strata, and because the trial was not designed to evaluate long-term survival or disease outcomes and was not stratified for relevant prognostic factors, it is difficult to draw any firm conclusions from the data in this trial alone.

6.13 The ESC noted that in Study 782, the upper confidence interval of the hazard ratio of 1.01 was also less than the pre-specified non-inferiority margin of 1.15, demonstrating non-inferiority to placebo for overall survival.

6.14 In Studies 782, 297, 161 and 145, while there were no statistically significant differences in median time to disease progression (and/or death) for patients treated with darbepoetin alfa compared to placebo, the interpretation of the results may differ across the trials. It was noted that for Studies 782 and 297, HRs for time to progression (and/or deaths) were < 1 (with upper CIs close to 1) indicating lower risk

for darbepoetin alfa versus placebo, for Studies 161 and 145 they were >1 (with upper CIs exceeding the nominated non-inferiority margin in Study 782 of 1.15), indicating potentially worse PFS for those treated with darbepoetin alfa in these trials.

6.15 The ESC noted that in Study 782, darbepoetin alfa was able to demonstrate non-inferiority versus placebo for time to progression as the upper CI of 1.04 was less than the nominated non-inferiority margin of 1.15.

6.16 Table 7 summarises transfusion outcomes in the trials, which was proportion of patients receiving RBC transfusion from Week 5 to the end of treatment period (EOTP) for most of the included trials. The main Study 782 and Katsumata 2009 also reported a composite outcome of RBC transfusion or Hb ≤ 80 g/L from Week 5 to the end of treatment period, termed “transfusion trigger” in Katsumata 2009.

Table 7: Results of proportion of patients receiving RBC transfusion (A) or achieving transfusion trigger (B) – trial report values

Trials	Outcomes	DA	Placebo	RD (95% CI)	OR (95% CI)	RR# (95%CI)
A: Proportion of patients receiving RBC transfusion						
<i>Main safety and dosage regimen trial</i>						
Study 782 ^A	n/N (%)	281/1680 (16.7%)	189/836 (22.6%)	-6% (-9%, -3%)	0.69 (0.55, 0.85) ^c	0.74 (0.63, 0.87)
<i>Main efficacy trials</i>						
Study 297 ^A	n/N (%)	39/156 (25.0%)	74/158 (46.8%)	-22% (-32%, -12%)	0.38 (0.23, 0.61)	0.53 (0.39, 0.73)
	K-M % (95% CI)	21% (15%, 28%)	51% (43%, 60%)	-24% (-35%, -13%)	-	-
Study 161 ^A	n/N (%)	52/174 (29.9%)	80/170 (47.1%)	-17% (-27%, -7%)	0.48 (0.31, 0.75)	0.64 (0.48, 0.84)
	K-M % (95% CI)	29% (23%, 36%)	50% (43%, 57%)	-17% (-27%, -7%)	-	-
Study 114 ^A	n/N (%)	6/22 (27.3%)	5/11 (45.5%)	-18% (-53%, 17%)	0.45 (0.10, 2.04)	0.6 (0.23, 1.54)
	K-M % (95% CI)	27% (9%, 46%)	45% (16%, 75%)	NR	-	-
Study 291 (S1) ^A	n/N (%)	4/17 (23.5%)	22/51 (43.1%)	-20% (-44%, 5%)	0.41 (0.12, 1.42)	0.55 (0.22, 1.36)
	K-M % (95% CI)	28% (4%, 51%)	46% (32%, 61%)	NR	-	-
Study 232 ^A	n/N	44/193 (22.8%)	72/193 (37.3%)	-15% (-24%, -5%)	0.50 (0.32, 0.77)	0.61 (0.44, 0.84)
	K-M % (95% CI)	24% (18%, 30%)	41% (34%, 49%)	-16% (-26%, -7%)	-	-
Katsumata 2009*	n/N (%)	7/103 ^d (7.28%)	20/104 ^d (19.2%)	-12%(-21%, -3%) P=0.015	0.31 (0.12, 0.76)	0.35 (0.16, 0.80)
Suzuki 2008*	n/N (%)	6/41 ^d (14.8%)	6/42 ^d (13.6%)	0% (-15%, 15%)	1.03 (0.30, 3.50)	1.02 (0.36, 2.92)
Supplementary trials^a						
Study 231 ^A		DA 500µg Q3W	DA 2.25 µg/kg QW			
	n/N (%)	76/353 (21.5%)	96/352 (27.3%)	-6% (-12%, 1%)	0.73 (0.52, 1.03)	0.79 (0.61, 1.02)
	K-M % (95% CI)	23% (19%, 28%)	30% (25%, 35%)	-7% (-14%, 0.1%)	-	-
Study 156 ^A		DA + IV iron	DA + Std practice			
	n/N (%)	16/200 (8.0%)	36/196 (18.4%)	-10% (-17%, -4%)	0.39 (0.21, 0.72)	0.44 (0.25, 0.77)

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Trials	Outcomes	DA	Placebo	RD (95% CI)	OR (95% CI)	RR# (95%CI)
	K-M % (95% CI)	9% (5%, 14%)	20% (14%, 26%)	-11% (-18%, -3%)	-	-
B: Proportion of patients reaching the transfusion trigger (Transfusion trigger defined as Hb ≤ 80 g/L or patient received a RBC transfusion)						
		DA n/N (%)	Placebo n/N (%)			
Study 782 [^]	Primary Analysis Set	342/1680 (20.4%)	223/836 (26.7%)	-6% (-10%, -3%)	0.70 (0.57, 0.86)^d	0.76 (0.66, 0.88)
	Sub-group – screening Hb<100g/L	226/765 ^b (29.5%)	146/396 ^b (36.9%)	-7% (-13%, -2%)	0.71 (0.55, 0.93)^d	0.80 (0.68, 0.95)
	Sub-group screening Hb≥100g/L	116/752 ^b (15.4%)	77/368 ^b (20.9%)	-5% (-10%, -1%)	0.69 (0.50, 0.96)^d	0.74 (0.57, 0.96)
Katsumata 2009 [^]	n/N (%)	29/103 ^d (28.5%)	63/104 ^d (60.1%)	-32% (-45%, -20%)	0.26 (0.14, 0.46)	0.46 (0.33, 0.66)

Grey shading indicate data previously seen by the PBAC.

Abbreviations: DA = darbepoetin alfa; K-M=Kaplan-Meier; RBC = red blood cell; NR=not reported.

[^] from Week 5 to end of treatment

* time points for measuring the outcomes were not reported in the trial abstracts.

unstratified RR estimated using STATA V.14.0 during the evaluation.

^a The November 2007 resubmission did not present these results for the supplementary trials.

^b Subjects on-study as of Study Day 29.

^c Study 782: Stratified odds ratio; stratification factors were geographic region, histology, screening Hb. Unstratified RR estimated during evaluation is 0.74 (0.63, 0.87).

^d n back calculated from reported percentages during the evaluation as these numbers were not reported in the abstract.

Source: Table 2.31, pp99; 102-111 of the resubmission; Table 2.66, p136 of the resubmission.

6.17 The ESC noted that a statistically significant difference in the transfusion incidence from Week 5 to end of treatment period was observed between darbepoetin alfa and placebo in Studies 782, 297, 161, and 232, however no significant differences in this outcome were observed in Studies 114 and 291 (S1).

6.18 Table 8 summarises results of proportion of patients achieving a Hb response of ≥20 g/L increase in Hb from baseline. The ESC noted that this trial outcome was also a key input into the economic model. It was also noted that Hb response was not a prospectively defined outcome in Study 231 and Study 156. Results for this endpoint were generated for the November 2007 resubmission to allow a comparison with the other trials, and are also reported in Table 8.

Table 8: Results of proportion of patients achieving Hb response (≥ 20 g/L increase from baseline) – trial report values for main efficacy trials and generated for supplementary trials

Trials	Outcomes	Darbepoetin alfa	Placebo	RD (95% CI)	OR (95% CI)
Main efficacy trials					
Study 297	n/N	66/156 (42.3%)	22/158 (13.9%)	28% (19%, 38%)	4.53 (2.61, 7.87)
	K-M % (95% CI)	48% (39%, 56%)	18% (11%, 24%)	29% (18%, 40%)	-
Study 161	n/N	93/174 (53.4%)	27/170 (15.9%)	38% (28%, 47%)	6.08 (3.66, 10.10)
	K-M % (95% CI)	58% (50%, 65%)	16% (10%, 22)	41% (31%, 50%)	-
Study 114	n/N	12/22 (54.5%)	1/11 (9.1%)	45% (19%, 72%)	12.00 (1.30, 110.52)
	K-M % (95% CI)	55% (34%, 76%)	10% (0%, 29%)	NR	-
Study 291 (S1)	n/N	7/17 (41.2%)	6/51 (11.8%)	29% (4%, 54%)	5.25 (1.45, 19.03)
	K-M % (95% CI)	48% (22%, 74%)	14% (3%, 24%)	NR	-
Suzuki 2008	n/N (%)	(67.7%)	(11.8%)	56% (39%, 74%)	15.94 (5.09, 49.95)
Supplementary trials					
Study 231		DA 500μg Q3W	DA 2.25 μg/kg QW		
	n/N (%)	163/348 (46.8%)	164/348 (47.1%)	0% (-8%, 7%)	0.99 (0.73, 1.33)
Study 156	Study 156	DA + IV iron	DA + Std practice		
	n/N (%)	123/196 (62.8%)	108/195 (55.4%)	7% (-2%, 17%)	1.36 (0.91, 2.03)

Grey shading indicate data previously seen by the PBAC.

Abbreviations: DA=darbepoetin alfa; Hb=haemoglobin; K-M=Kaplan-Meier; NR=not reported.

Source: pp.102-109 of this resubmission; Table 2.91, p150 of resubmission (sourced from Table B.6.17, p135 of the November 2007 resubmission).

- 6.19 The ESC noted a statistically significant differences in the proportion of patients with Hb response was observed between darbepoetin alfa and placebo in all the main efficacy trials (with prospectively defined Hb responses).
- 6.20 The resubmission reported QoL outcomes in the form of Functional Assessment of Cancer Therapy-Fatigue subscores (FACT-F). The resubmission nominated a change of ≥ 3 points on the FACT-F scale as being minimally clinically important. No significant differences in changes in FACT-F score were observed between darbepoetin alfa and placebo treated patients in the included trials. Mean differences between darbepoetin alfa and placebo treatment arms were small and were all less than the nominated minimally clinically important difference (MCID) of 3 points. The ESC noted that the PSCR presented additional evidence to support a link between Hb level and QoL:
- eAQUA observational study, a univariate exploratory analysis found improved QoL at week 9 for patients with Hb increase ≥ 10 g/L compared with < 10 g/L (OR=1.79, 95% CI: 1.26-2.56);
 - Study 114 and Study 291 (S1), change in FACT-F scale and Hb were correlated;
 - Study 297 significantly more darbepoetin alfa patients had $\geq 10\%$, $\geq 15\%$, $\geq 20\%$ or $\geq 25\%$ improvements in FACT-F compared with placebo;
 - Study 161, there were significantly greater increases in FACT-F scores with darbepoetin alfa when adjusted for baseline covariates, and stratification factors.

Comparative harms

- 6.21 The incidence of any adverse events (AEs), serious AEs, and deaths were generally similar between the darbepoetin and placebo treatment groups in Study 782 and the

main efficacy trials. Exceptions were in Study 114, the proportion of patients with serious AEs was marginally significantly higher with placebo compared to darbepoetin alfa, and the proportion of patients with treatment-related AEs tended to be higher for darbepoetin alfa although not significantly different compared to placebo. The most frequently reported AEs in the darbepoetin alfa and placebo groups were nausea, fatigue, neutropenia and vomiting.

- 6.22 Three AE types (hypertension, seizure/convulsions and thromboembolic events) were prospectively defined as being of interest in subjects treated with darbepoetin alfa. These AEs are summarised in Table 9. The ESC noted that thromboembolic events occurred at a consistently higher rate in patients treated with darbepoetin alfa compared to placebo, however the differences did not reach statistical significance in the individual trials. Pooled results were not presented in the resubmission. When AEs reported in placebo controlled trials in Table 9 were pooled during the evaluation, thromboembolic events were found to be significantly higher for darbepoetin alfa versus placebo (RR (95%CI): 1.44 (1.10-1.89)).

Table 9: Summary of adverse events of historical interest (hypertension, seizure, thromboembolic events) in the trials

Trial ID	Tx group	Hypertension	Seizure	Thromboembolic events
Main safety and dosage regimen trial				
Study 782	DA	41/1685 (2.2%)	9/1685 (0.5%)	89/1685 (4.7%)
	PBO	26/833 (3.1%)	8/833(1.0%)	34/833 (4.1%)
Main efficacy trials				
Study 297	DA	9/155 (5.8%)	0/155 (0%)	7/155 (4.5%)
	PBO	6/159 (3.8%)	1/159 (0.6%)	5/159 (3.1%)
Study 161	DA	8/175 (4.6%)	0/175 (0%)	9/175 (5.1%)
	PBO	5/169 (3.0%)	0/169 (0%)	3/169 (1.8%)
Study 114	DA ^a	2/55 (3.6%)	0/55 (0%)	1/55 (1.8%)
	PBO	1/11 (9.1%)	0/11 (0%)	0/11 (0%)
Study 291 (S1)	DA ^a	4/198 (2.0%)	0/198 (0%)	16/198 (8.1%)
	PBO	0/51 (0%)	0/51 (0%)	4/51 (7.8%)
Study 232	DA	6/194 (3.1%)	3/194 (1.5%)	18/194 (9.3%)
	PBO	4/192 (2.1%)	1/192 (0.5%)	11/192 (5.7%)
Study 145	DA	18/301 (6.0%)	4/301(1.3%)	26/301 (8.6%)
	PBO	15/296(5.1%)	9/296(3.0%)	15/296 (5.1%)
Supplementary trials				
Study 231	DA 500µg Q3w	8/353 (2.3%)	1/353 (0.3%)	28/353 (7.9%)
	DA 2.25µg/kg Qw	12/352 (3.4%)	1/352(0.3%)	27/352(7.8%)
Study 156	DA + IV iron	2/203 (1.0%)	0/203(0%)	12/203 (5.9%)
	DA	5/193 (2.6%)	1/193(0.5%)	12/193 (6.2%)

Abbreviations: DA=darbepoetin alfa; PBO=placebo.

^a Darbepoetin alfa treatment groups combined.

Source: compiled during the evaluation from results reported in Tables 2.42- Table 2.63; pp.129-134 of resubmission.

Broader literature on ESAs

- 6.23 The resubmission discussed (pp151-152) results from published systematic reviews and meta-analyses comparing darbepoetin alfa with placebo in patients with a baseline Hb level ≤100g/L. The results from the included meta-analyses Boccia et al 2016 and Pirker et al 2016 confirm that darbepoetin alfa is more effective than

placebo at increasing serum Hb levels and at reducing the need for transfusion in patients with CIA when treatment is initiated at Hb \leq 100 g/L.

- 6.24 The resubmission also noted several meta-analyses of darbepoetin alfa RCTs in the setting of CIA where an increase in mortality and disease progression was not observed (Ludwig et al 2009, Vanteenkiste et al 2012, and Grant et al 2013). However all three meta-analyses, had concluded that the risk for thromboembolic events to be significantly higher for darbepoetin alfa versus placebo.
- 6.25 The ESC noted a recent Cochrane review reported by Tonia et al 2012⁵ of 91 trials with 20,102 participants for epoetin and darbepoetin found that the risk of venous thromboembolism (VTE) was increased in patients receiving ESAs (RR (95%CI): 1.52 (1.34-1.74)). There was strong evidence that ESAs increase mortality during active therapy (on-study mortality, hazard ratio (HR (95% CI): 1.17 (1.06-1.29)), and modest evidence that they increase overall mortality (HR (95%CI): 1.05 (1.00-1.11)). However, when the analysis was restricted to trials of patients receiving chemotherapy, there was only a trend toward higher on-study (OR (95%CI): 1.10 (0.98-1.24)) and overall mortality (OR (95%CI): 1.04 (0.98-1.11)), neither of which was statistically significant. In trials of no antineoplastic therapy, use of ESAs significantly increased both on-study mortality (OR (95% CI): 1.34 (1.07-1.66)) and overall mortality (OR (95%CI): 1.23 (1.04-1.45)). Use of ESAs significantly increased the risk of hypertension (RR 1.30, 95% CI 1.08-1.56) and thrombocytopenia/haemorrhage (RR 1.21, 95% CI 1.04-1.42). It was noted that all darbepoetin alfa placebo-controlled trials presented in this resubmission were included in Tonia et al (2012) review with the exception of Study 782 which was only completed in 2018. The systematic review had also included trials irrespective of the dose of the ESA used, including dosages which are outside of the market authorisations of the respective ESAs. These trials were by contrast, excluded from the evidence in this resubmission. The PSCR argued that the broader literature on ESAs were not relevant to darbepoetin alfa as historically ESAs have been used differently in trials and clinical practice compared with current recommendations. The ESC considered the results of the broader literature remained relevant, particularly when restricted to trials of patients receiving chemotherapy.
- 6.26 In view of meta-analyses results on safety of ESAs, data from a recent safety trial for epoetin was also reviewed during the evaluation (Leyland Jones et al 2016). In this trial, 2098 women with anaemia undergoing chemotherapy for metastatic breast cancer and who had haemoglobin \leq 110g/L were randomly assigned to epoetin 40,000 IU subcutaneously once a week or best standard of care. The primary end point, median progression free survival based on investigator determined disease progression was 7.4 months in both groups (HR (95%CI): 1.089 (0.988 to 1.200)); while not statistically significant, the upper bound 95% CI had exceeded the pre-specified non-inferiority margin of 1.15. Median overall survival at clinical cutoff (1,337 deaths)

⁵ Tonia, T, et.al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev 2012, Issue 12.Art.No.:CD003407.DOI:10.1002/14651858.CD003407.pub5.

was 17.2 months in the epoetin and 17.4 months in the best standard of care group (HR (95%CI): 1.057 (0.949 to 1.177)), median time to tumour progression was 7.5 months in both groups (HR (95% CI: 1.094 (0.991 to 1.209)). While the median PFS per independent review committee–determined disease progression was 7.6 months in both groups (HR (95% CI): 1.028 (0.922, 1.146)) and the upper bound did not exceed pre-specified non-inferiority margin, the investigators concluded that the trial did not achieve non-inferiority objective in ruling a 15% increased risk in disease progression/death. The PSCR argued that data for a trial of a different treatment, epoetin, were not relevant for this resubmission.

Benefits/harms

6.27 A summary of the comparative benefits and harms for darbepoetin versus standard management (or placebo in the trials) is presented in Table 10.

Table 10: Summary of comparative benefits and harms for darbepoetin alfa and PBO

Trial	Darbepoetin alfa, n/N	PBO, n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Darbepoetin alfa	PBO	
Benefits						
Dichotomous outcome: Proportion of patients receiving RBC transfusion from Week 5 to the end of treatment period (EOTP)						
Study 782	281/1680	189/836	0.74 (0.63, 0.87)	16.7	22.6	-6% (-9%, -3%)
Study 297	39/156	74/158	0.53 (0.39, 0.73)	25.0	46.8	-22% (-32%, -12%)
Study 161	52/174	80/170	0.64 (0.48, 0.84)	29.9	47.1	-17% (-27%, -7%)
Study 232	44/193	72/193	0.61 (0.44, 0.84)	22.8	37.3	-15% (-24%, -5%)
Katsumata 2009 [^]	7/103	20/104	0.35 (0.16, 0.80)	7.2	19.2	-12% (-21%, -3%)
Dichotomous outcome: Proportion of patients achieving Hb response (≥20 g/L increase from baseline)						
Study 297	66/156	22/158	3.04 (1.98, 4.67)	42.3	13.9	28% (19%, 38%)
Study 161	93/174	27/170	3.37 (2.32, 4.89)	53.4	15.9	38% (28%, 47%)
Study 114	12/22	1/11	6.00 (0.89, 40.41)	54.5	9.1	45% (19%, 72%)
Study 291(S1)	7/17	6/51	3.50 (1.36, 8.98)	41.2	11.8	29% (4%, 54%)
Suzuki 2008	28/41	5/42	5.74 (2.46, 13.40)	67.7	11.8	56% (39%, 74%)
Time-to-death						
Study 161	Darbepoetin alfa		PBO		HR (95% CI)	
Median (mths)	30.23		41.77		1.36 (1.02, 1.82)	
Harms						
	Darbepoetin alfa	PBO	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Darbepoetin alfa	PBO	
Thromboembolic events						
Pooled across Studies 782, 297, 161, 114, 291 (S1), 145 and 232	77/1078	38/878	1.44 (1.10, 1.89)	6.0	4.2	2% (1%, 3%)

Grey shading indicate data previously seen by the PBAC.

[^] time points for measuring this outcome was not reported so may not be comparable to the other trials.

* Study 782: Patients were followed until death or until the protocol-specified number of deaths occurred.

Median duration of follow-up: Studies 297, 161, 114 ~ 16 weeks; Study 291(S1) = 12 weeks; Study 232 ~ 19 weeks; Suzuki 2008 NR.

HR = hazard ratio; NR= not reported; PBO = placebo; RD = risk difference; RR = risk ratio

Source: compiled during the evaluation based on efficacy results reported in the re-submission.

- 6.28 On the basis of direct evidence presented by the resubmission, for every 100 patients treated with darbepoetin alfa in comparison to placebo and over a median follow-up duration of 12-19 weeks:
- The results varied across the trials, but between approximately 6 and 22 fewer patients would have RBC transfusions from Week 5 to the end of treatment period.
 - The results varied across the trials, but between approximately 28 and 56 additional patients would have Hb response (defined as Hb increase ≥ 20 g/L).
- 6.29 On the basis of the direct evidence from Study 782, Study 297, Study 145 (see Table 5), there was no difference in overall survival for darbepoetin alfa compared with placebo. However on the basis of direct evidence from Study 161, there was a reduction in median overall survival of 11.54 months over a median duration of follow up of 25-33 months with darbepoetin alfa compared with placebo.
- 6.30 The differences between thromboembolic events did not reach statistical significance in the individual trials but was found to be significantly higher with darbepoetin alfa compared to placebo when results across placebo controlled trials were pooled. On the basis of pooled evidence from Studies 782, 297, 161, 114, 291(S1), 145 and 232, for every 100 patients treated with darbepoetin alfa in comparison to placebo and over a median follow-up duration of 12-19 weeks, approximately 2 additional patients would have thromboembolic events.
- 6.31 The broader literature (including results of trials for epoetin analogues) also suggests the risk of venous thromboembolism to be significantly increased in patients receiving either darbepoetin alfa or epoetin analogues.

Clinical claim

- 6.32 The resubmission claimed that darbepoetin alfa was superior in terms of effectiveness compared to placebo (standard medical management). The efficacy conclusions were adequately supported for haemoglobin and transfusion outcomes, however, it was noted that patient-reported outcomes on changes in QoL such as the FACT-F scores did not find darbepoetin alfa to be significantly better than placebo. The ESC noted that the PSCR presented additional evidence to support a link between Hb level and QoL.
- 6.33 The resubmission claimed that darbepoetin alfa was non-inferior in terms of safety, overall mortality and PFS, compared to placebo (standard medical management). This claim does not appear to be supported by data presented in the resubmission, pooled results of placebo controlled trials included in this resubmission indicates significantly higher incidence of thromboembolic events for darbepoetin alfa versus placebo.
- 6.34 The broader literature for ESAs also indicate evidence that ESAs increase mortality during active therapy (on-study mortality, HR (95%CI): 1.17 (1.06-1.29)), and modest evidence that they increase overall mortality (HR (95%CI): 1.05 (1.00-1.11)). However, when the analysis was restricted to trials of patients receiving chemotherapy, there was only a trend towards higher on-study (OR (95%CI): 1.10 (0.98-1.24)) and overall

mortality (OR (95%CI): 1.04 (0.98-1.11)), neither of which was statistically significant (Cochrane 2012 review reported by Tonia et al 2012). The PSCR argued that the broader literature on ESAs were not relevant to darbepoetin alfa as historically ESAs have been used differently in trials and clinical practice compared with current recommendations. The ESC considered the results of the broader literature remained relevant to safety deliberations.

- 6.35 Study 782 attempted to address the uncertainty of ESAs on overall survival or progression-free survival in lung cancer patients (specifically patients diagnosed with NSCLC). The results of the trial supported a conclusion of non-inferior safety between those treated with darbepoetin alfa versus placebo for both overall mortality (HR (95%CI): 0.92 (0.83, 1.01) and progression free survival (HR (95%CI): 0.95 (0.87, 1.04)), meeting the trial's pre-specified non-inferiority margin of 1.15. The ESC noted this conflicts with results of a trial conducted in patients with other cancers.
- 6.36 In Study 161, conducted in patients with lymphoproliferative cancers, overall mortality was significantly worse for those treated with darbepoetin alfa (HR (95%CI): 1.36 (1.02, 1.82)). Both the NCCN 2018 guidelines and the FDA do not recommend ESA for patients receiving myelosuppressive chemotherapy with curative intent. The EMA also recommended that blood transfusions are preferred over ESAs in cancer patients who have chemotherapy-related anaemia and a "reasonably long life expectancy" (EMA 2008). It is however difficult to draw any firm conclusions from Study 161 alone as increased risk in subjects receiving darbepoetin alfa was limited to a small number of subjects in the heavily pre-treated strata (i.e., subjects who received ≥ 2 previous lines of chemotherapy or 1 line of chemotherapy and a stem-cell transplant). The trial was also not designed to evaluate long-term survival or disease outcomes and was not stratified for relevant prognostic factors.
- 6.37 The ESC considered that variation in overall survival and thromboembolic events across trials for different cancers and at different Hb levels suggested that the claim of non-inferior safety may not be supported.
- 6.38 The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data for Hb and transfusion outcomes. The PBAC considered that the additional evidence presented in the PSCR suggested there may be a link between Hb level and QoL.
- 6.39 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

- 6.40 The resubmission presented a stepped economic evaluation comparing darbepoetin alfa versus standard care. This is the first submission for darbepoetin alfa in which a cost-utility model has been presented. The November 2007 resubmission presented cost-effectiveness analyses with transfusion and haematological outcomes. Table 11 summarises the model structure and rationale as well as steps in the stepped economic evaluation.

Table 11: Summary of model structure and rationale

Component	Summary
Time horizon	3 years in the model base case vs. 15 weeks in Study 231 (source of Hb response data for darbepoetin alfa).
Steps in the stepped economic evaluation	<p>1. Model duration of 21 weeks (i.e., to the end of chemotherapy (assumed to be 18 weeks), plus one additional dose (3 weeks) of darbepoetin alfa treatment for responders). Cost per Hb responder analysis used Hb response (defined as Hb increase \geq 20 g/L) from the darbepoetin alfa fixed dose arm of Study 231 and assumed zero Hb responders in the standard care arm. This is not appropriate (see further discussions below). Transfusion response was based on inputs from the Wilson et al (2007) economic model. Each RBC transfusion was assumed to increase Hb by 10g/L lasting for one treatment cycle.</p> <p>2. Three year model, including mortality risk (elevated risk compared to the general population), but similar mortality across the two treatment arms. Discounting rate of 5% per annum applied to costs.</p> <p>3. Application of utility weights to each health state. Discounting rate of 5% per annum applied to costs and outcomes.</p>
Outcomes	QALYs
Methods used to generate results	Markov microsimulation model (with results generated using 1000 simulations)
Health states	<p>Hb levels (one for each of 'On ESA' and 'Off chemo/ESA' health states)</p> <ol style="list-style-type: none"> 1. Hb < 80 g/L 2. Hb 80-90 g/L 3. Hb 90-100 g/L 4. Hb 100-110 g/L 5. Hb 110-120 g/L <p>Death</p>
Cycle length	3 weeks
Transition probabilities	Proportion of patients attaining a Hb response for darbepoetin alfa was derived from Study 231; other key inputs were derived from modelled economic evaluation reported by Wilson et al. (2007).

Abbreviations: ESA = erythropoiesis-stimulating agent, Hb = haemoglobin

Source: Table 3.1, pp. 161-162 of the resubmission

6.41 The resubmission's modelled economic evaluation largely follows (structure and inputs) a model developed for NICE of ESAs (epoetin alfa, epoetin beta and darbepoetin) versus standard care in CIA (referred in the literature as the Birmingham epo model, reported by Wilson et al 2007⁶). The ESC noted that, while a number of trials were examined in the resubmission, the only results relied on in the resubmission's modelled economic evaluation was the result for Hb response for darbepoetin alfa from the fixed dose single arm of Study 231. As Study 231 did not include a placebo arm, the results for standard management arm of the resubmission's model followed inputs from Wilson et al (2007) which came from the literature. The ESC considered that this means the resubmission's model was not based on the clinical outcomes presented in the resubmission. The PSCR stated that RBC transfusion data from Study 782 was not applicable to the model because the

⁶ NICE technology appraisal guidance 142 (2008) recommended erythropoietin analogues (epoetin alfa, beta, and darbepoetin alfa) for cancer treatment induced anaemia in women having platinum-based chemotherapy for ovarian cancer and who have symptoms associated with anaemia and a haemoglobin concentration of 80g/L or lower. The guidance stated that clinicians may also consider ESA for people who cannot have blood transfusions and who have profound cancer treatment related anaemia that is likely to affect survival. This was later replaced by NICE technical guidance TA323 in 2014, which recommended the ESAs for use within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

endpoint was a composite outcome and the proportion of patients with transfusions is not the same as the rate of transfusions. The ESC noted that although probabilities and rates are different, the rate of RBC transfusions assumed in the base case overestimated the proportion of patients who received RBC transfusion in the main trial evidence (Study 782). The ESC noted that the RBC transfusion rate was a key driver of the model and considered that the impact on the model was high and favoured darbepoetin alfa.

- 6.42 The resubmissions model was compared with published economic evaluations including Wilson et al (2007), a Swedish model (Borg et al 2008) and a Canadian model (sourced during the evaluation, Klarenbach et al 2010).
- Notably, the models presented different perspectives on survival between ESAs and standard care. Wilson et al (2007), Borg et al 2008 and the resubmission's model had assumed no difference between the strategies for survival in the base case, whereas the Canadian model reported by Klarenbach et al 2012 assumed worse survival for those treated with epoetin (data from systematic review reported by Tonelli et al, 2009⁷). The resubmission claimed the assumption of no survival gain for darbepoetin alfa over standard care to be conservative. However, given the broader literature and Study 161 (which was part of the included trials) showing potentially reduced survival for patients on ESAs versus standard management particular if ESAs are used outside of practice guidelines, the ESC did not consider this assumption to be conservative.
 - The resubmission's model does not include either costs or consequences of AEs for darbepoetin alfa. The model reported by Klarenbach et al 2010 did take into account potential AEs of ESAs including thromboembolic events. The model reported by Wilson et al 2007 also included under ESA treatment costs, the cost of managing severe adverse events (SAEs), with an assumed 5% probability of occurrence. Costs of thromboembolic events were included in the model in the November 2007 resubmission of darbepoetin alfa. While the individual trials included by the resubmission did not find any statistically significant differences in thromboembolic events, the pooled trial data and data from the broader literature suggests darbepoetin and ESAs treatments to be associated with significantly higher incidences of thromboembolic events. The ESC considered that excluding costs associated with AEs may under estimate costs for darbepoetin alfa treatment.
- 6.43 The modelled economic evaluation also relies on a key assumption that darbepoetin alfa will improve patient QoL by allowing more rapid improvements in Hb levels, while darbepoetin alfa is associated with a reduction in RBC transfusions; the trial evidence on FACT-F scores did not find any significant differences between darbepoetin alfa and

⁷ Tonelli M, Hemmelgarn B, Reiman T et al. Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. *CMAJ* 2009; 180(11): E62-E71.

standard management with respect to QoL. The ESC noted that the PSCR presented additional evidence to support a link between Hb level and QoL (see paragraph 6.18).

6.44 In Step 2 of the stepped economic evaluation, the resubmission presented a cost-effectiveness analysis estimating incremental cost per Hb responder (defined as Hb increase ≥ 20 g/L). However, the ESC considered the estimation was flawed in that while it tracked Hb responders to darbepoetin alfa, it had assumed zero response for patients in the standard care arm. The ESC considered that this was inappropriate. A proportion of patients in both arms of the model are assumed to receive RBC transfusions, which will increase Hb. Placebo group Hb responses in the included trials were also not zero and had ranged between 9.1% to 15.9%, some of the Hb response attributed to darbepoetin alfa from Study 231 would have also been from patients who received a transfusion.

6.45 The PBAC noted the key drivers of the model summarised in Table 12.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Hospitalisation costs of RBC transfusion.	Patients are assumed to incur additional hospitalisation costs for RBC transfusions, costs were estimated from AR-DRG costs for hospitalisations associated with cancer types in the darbepoetin alfa trials (cost: \$██████ per transfusion). As more RBC transfusions occur in the standard care arm of the model, this is a main cost offset for darbepoetin alfa treatment. Not all patients will require additional hospitalisation days for RBC transfusions. Some patients may already be hospitalised for chemotherapy and depending on the total units of RBC required, many patients may receive transfusions in an outpatient setting. Therefore, the assumption of \$██████ per transfusion is considered overly high. By comparison the MBS cost for transfusions (item number: 13706, assuming no blood collection) is only \$83.35 per episode.	High, favours darbepoetin alfa.
RBC transfusion rate for standard care	Sourced from the Birmingham epo model (Wilson et al. 2007). The proportions of patients with transfusions from the model were much higher than reported in the clinical trial evidence, Additional sensitivity analysis were performed during the evaluation using lower rates reported in the clinical trials.	High, favours darbepoetin alfa.
Chemotherapy duration	The model in the resubmission assumed a course of chemotherapy to be 18 weeks or six 3-weekly cycles. The number of chemotherapy cycles may be slightly over-estimated as the darbepoetin alfa doses reported in the trials were lower (median of ██████ cycles; Table 14-5.1, p163 of CSR for Study 782; median and maximum of ██████ cycles in Study 231; Table 11-2, p155 of CSR for Study 231).	Moderate, favours darbepoetin alfa.
Utilities	Base case utilities in the model were sourced from Wilson et al 2012. They were originally based on utility values from the Ortho Biotic (OB) company submission to NICE measured using the time trade off (TTO) methodology. In sensitivity analysis, the resubmission used alternate standard gamble (SG) utility values from a UK study (Lloyd et al, 2008), which showed darbepoetin alfa to be less costly but also generating fewer QALYs.	Moderate, favours darbepoetin alfa.

Abbreviations: RBC = red blood cell;
Source: constructed during the evaluation.

6.46 Table 13 summarises results from the stepped economic evaluation.

Table 13: Results of the stepped economic evaluation

Step and component	Darbepoetin alfa	Standard care	Increment
Step 1: 21-week costs and outcomes			
Costs	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
Hb responders	0.623	0	0.623
Incremental cost/extra Hb responder			[REDACTED]
Step 2: time horizon extended to 3 years; include mortality risk, discounting			
Costs	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
Hb responders	0.553	0	0.553
Incremental cost/extra Hb responder			[REDACTED]
Step 3: utility weights applied; discounting			
Costs	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
QALYs	0.8950	0.8704	0.0246
Incremental cost/extra QALY gained (base case)			[REDACTED]
Step 3: Truncated to 21 weeks			
Costs	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
QALYs	0.2289	0.1919	0.037
Incremental cost/extra QALY gained			[REDACTED]

Source: Tables 3.25, 3.27, 3.29, pp.210, 211, 213 of the resubmission.

6.47 The ESC considered that, due to the assumption of a zero Hb response for patients in the standard care arm, Step 1 and Step 2 of the economic evaluation presented in Table 13 were not informative.

6.48 Results truncated to 21 weeks (till the end of treatment with darbepoetin alfa) in Table 13 indicated that the model was not sensitive to assumptions around time horizon, with the 21 week results reporting similar costs but fewer QALYs for both treatment strategies. The difference between darbepoetin alfa and standard management showed a smaller cost saving for darbepoetin alfa but slightly higher increase in QALYs.

6.49 Table 14 summarises disaggregated costs for items included in the economic evaluation.

Table 14: Health care resource items: disaggregated summary of cost impacts

Resource item	Darbepoetin alfa cost	Standard care cost	Incremental cost
Pharmaceutical products			
Darbepoetin alfa	\$ [REDACTED]	\$0	\$ [REDACTED]
Chemotherapy	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
Medical services			
Hospital admissions for transfusions	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
Blood products	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
Overall total	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]

Source: compiled during the evaluation from TreeAge model.

- 6.50 The ESC noted that Table 14 illustrates the cost assumed for hospital admissions for transfusions to be a main driver of the model, with cost savings from hospitalisation for transfusions (\$ [REDACTED]) more than offsetting the additional costs for darbepoetin alfa (\$ [REDACTED]). The other main cost savings for darbepoetin alfa treatment is the cost of blood products avoided.
- 6.51 The cost of \$ [REDACTED] per transfusion was estimated from average hospital AR-DRG costs for hospitalisations associated with cancer types included in darbepoetin alfa trials, with no consideration of outpatient treatment. Some patients may already be hospitalised for chemotherapy and depending on the total units of RBC required, many patients may receive transfusions in an outpatient setting (the MBS cost (item 13706) is \$83.35 per transfusion). The ESC considered it was unreasonable to assume that all patients would require additional hospitalisation episodes for RBC transfusions. The ESC considered that the cost of transfusions in the modelled economic evaluation was unreasonably high, and the probability of having transfusions uncertain.
- 6.52 Table 15 summarises sensitivity analyses for key parameters driving the results for incremental cost per QALY.

Table 15: Results of key sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case (3 years)	-\$ [REDACTED]	0.0246	[REDACTED]
Time horizon 21 weeks	-\$ [REDACTED]	0.037	[REDACTED]
Hb response rates			
DA Hb response assumed to have accrued over the 15-weeks duration of Study 231 (base case assumed that the reported result of 46.84% would apply to a 4 week duration)	\$ [REDACTED]	0.021	\$ [REDACTED]
RBC transfusion			
RBC transfusion rate for standard care 0.23 per 6 weeks from Study 782 placebo arm results (base case 0.31 per 4 weeks)	\$ [REDACTED]	0.0608	\$ [REDACTED]
RR darbepoetin alfa v standard care 0.74 as per Study 782 (base case 0.63)	-\$ [REDACTED]	0.0246	[REDACTED]
Transfusion cost			
Transfusion cost \$83.35 using outpatient MBS cost of transfusion (base case \$ [REDACTED]), blood cost unchanged	\$ [REDACTED]	0.0246	\$ [REDACTED]
Transfusion cost \$ [REDACTED]; 25% inpatients & 75% outpatients (base case \$ [REDACTED]), blood cost unchanged	\$ [REDACTED]	0.0246	\$ [REDACTED]
Chemotherapy duration			
Chemotherapy duration of 15 weeks (base case 18 weeks)	-\$ [REDACTED]	-0.0139	\$ [REDACTED] (DA less costly but also fewer QALYs)
Chemotherapy duration of 12 weeks (base case 18 weeks)	-\$ [REDACTED]	-0.0133	\$ [REDACTED] (DA less costly but also fewer QALYs)
Health State Utility Values			
Alternative utility values from Lloyd 2008 (base case Wilson et al 2007)	-\$ [REDACTED]	-0.0003 ^a	\$ [REDACTED] (DA less costly but also fewer QALYs)
Multivariate sensitivity analysis			
A: RBC transfusion rate for standard care 0.23 per 6 weeks from Study 782 placebo arm results (base case 0.31 per 4 weeks) AND B: RR of RBC transfusion for DA vs std care 0.74 based on Study 782 (base case 0.63)	\$ [REDACTED]	0.0608	\$ [REDACTED]
A + B AND C: DA Hb response assumed to have accrued over the 15-weeks duration of Study 231 (base case assumed that the reported result would apply to a 4 week duration)	\$ [REDACTED]	0.0157	\$ [REDACTED]
A + B + C AND D: Transfusion cost \$83.35 using outpatient MBS cost of transfusion (base case \$ [REDACTED]), blood cost unchanged	\$ [REDACTED]	0.0157	\$ [REDACTED]
A + B + C AND E: Transfusion cost \$ [REDACTED]; 25% inpatients & 75% outpatients (base case \$ [REDACTED]), blood cost unchanged	\$ [REDACTED]	0.0157	\$ [REDACTED]
A + B + C + E AND F: Using alternate health state utilities reported by Lloyd 2008.	\$ [REDACTED]	-0.0023	[REDACTED] (i.e., [REDACTED])
A + B + C + E AND G: Time horizon 21 weeks	\$ [REDACTED]	0.0263	\$ [REDACTED]

Abbreviations: DA=darbepoetin alfa; Hb= haemoglobin, RR=relative risk, std=standard care

^a The model applied an erroneous value of 0.773 for patients in the Hb 110-120 g/L health states (p227 of the resubmission). The correct value is 0.703 (Table 3 of Lloyd 2008). This correct value of 0.703 has been used here.

Source: generated during the evaluation using TreeAge model provided by the resubmission.

6.53 Results presented in Table 15 illustrate that the model was most sensitive to assumptions around hospitalisation costs associated with RBC transfusions, health state utilities, chemotherapy duration and the assumed Hb response rate. In multivariate analyses when RBC transfusion rate for standard care and relative risk reduction of RBC transfusion for darbepoetin alfa versus standard care were derived from Study 782 instead of values used in the Wilson et al (2007) economic evaluation and assuming a 25:75 split for inpatient/outpatient management of RBC transfusions the ICER increased to \$105,000/QALY to \$200,000/QALY from a base case result showing darbepoetin alfa [REDACTED]. The PSCR stated that the application of a 25:75 split for inpatient/outpatient management of RBC transfusions was not supported by hospital statistics and MBS data. The PSCR provided Australian Institute of Health and Welfare (AIHW) and Medical Benefits Schedule (MBS) data to support a 50:50 split of inpatient/outpatient management of RBC transfusions. The PSCR stated that under this scenario the ICER was less than \$15,000/QALY. The ESC noted that the AIHW and MBS data provided in the PSCR was for all patients who had received blood and blood products over 2015–2016 and hence was not specific for use in CIA. As such the ESC considered that the appropriate inpatient/outpatient management split remained uncertain as did the proportion of patients who would require a new admission for a RBC transfusion. The ESC noted that Wilson et al (2007) cited a large scale UK audit of blood transfusion requirements and anaemia in patients receiving cytotoxic chemotherapy (Barrett-Lee et al (2000)⁸). The audit stated that, of the patients requiring transfusion, 25% required an inpatient admission and an overnight stay. The pre-PBAC response argued that a retrospective observational study investigating the impact of a Patient blood management program on blood usage and patient outcomes in cancer patients in a US centre, from January 2008 through July 2013 supported the appropriateness of a 50:50 inpatient/outpatient management split (Gross et al 2016).⁹ The pre-PBAC response stated that there were 496 episodes of care that involved transfusions of RBCs for 251 unique patients. The 496 episodes involving RBC transfusion included 331 inpatients (67%) and 165 outpatients (33%). The PBAC noted that the Gross et al 2016 data provided in the pre-PBAC response was not specific for use in CIA.

6.54 When alternate health state utilities reported by Lloyd 2008 were used in the multivariate analyses in Table 15, standard care was dominant (i.e., less costly and more effective). The utility value for the highest Hb health state was lower at 0.703 in Lloyd 2008 compared to 0.749 in the base case from Wilson 2007, and patients

⁸ Barrett-Lee PJ, Bailey NP, O'Brien ME, Wager E. Large-scale UK audit of blood transfusion requirements and anaemia in patients receiving cytotoxic chemotherapy. *Br J Cancer* 2000;82:93–7.

⁹ Gross I, et al, Impact of a Patient Blood Management Program and an Outpatient Anemia Management Protocol on Red Cell Transfusions in Oncology Inpatients and Outpatients. *The Oncologist* 2016; 21:327–332.

spent a majority of their time in the highest Hb health states in the model, with darbepoetin alfa patients spending more time in the highest Hb health states relative to standard care patients.

Drug cost/patient/course: \$ [REDACTED]

- 6.55 The cost per patient per cycle of darbepoetin alfa 500 mcg was \$ [REDACTED] (public) and \$ [REDACTED] (private). Using the proportions of 44% public: 56% private based on AIHW hospital separation data, the weighted average cost per patient per cycle of darbepoetin alfa 500 mcg was \$ [REDACTED]. The weighted average cost per patient per treatment course of seven cycles was \$ [REDACTED], assuming the full dose of 500 mcg per cycle (Q3W).
- 6.56 The proposed PBS restriction allows lower doses of 300 mcg or 200 mcg Q3W to be used for patients with Hb above 100 g/L and who had previously responded. The cost per patient per cycle of darbepoetin alfa 300 mcg was \$ [REDACTED] (public) and \$ [REDACTED] (private). The cost per patient per cycle of darbepoetin alfa 200 mcg was \$ [REDACTED] (public) and \$ [REDACTED] (private).
- 6.57 The proposed prices in this resubmission are lower compared to the November 2007 resubmission. The ex-manufacturer prices in the November 2007 resubmission were \$ [REDACTED], \$ [REDACTED] and \$ [REDACTED] for the 500 mcg, 300mcg and 200mcg injections (private) respectively (same quantities as proposed in the current resubmission).

Estimated PBS usage & financial implications

- 6.58 This resubmission was considered by Drug Utilisation Sub Committee (DUSC).
- 6.59 The resubmission used an epidemiological approach starting from the incidences of malignancies that are commonly treated with myelotoxic chemotherapy regimens. In the base case analysis, the resubmission used the sum of all incident non-myeloid cancers from AIHW data, multiplied by the overall optimal chemotherapy utilisation rate of 49.1% from Jacob et al. (2015), an Australian study which aimed to estimate the optimal chemotherapy utilisation rate by cancer types based on guidelines review and modelling. The incidence of CIA was assumed to be the average of the estimates from two Australian data sources (Australian Cancer Anaemia Survey and Elements of Cancer Care study) in the base case.
- 6.60 The resubmission assumed uptake of darbepoetin alfa was 5% in 2019 and up to only 20% in 2023 and maintained for 2024. The number of doses for responders was assumed to be 5, with 3 doses for non-responders according to the PBS continuation rule.

Table 16: Estimated use and financial implications

	2019	2020	2021	2022	2023	2024
Estimated extent of use						
Number of patients treated [^]						
Estimated financial implications of darbepoetin alfa						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Copayments	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
Net financial implications						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Net cost of RBC transfusion	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to health budget	\$	\$	\$	\$	\$	\$

Abbreviations: RBC = red blood cell

[^] assumed uptake rates in 2019, 2020, 2021, 2022, 2023 and 2024 were: 5 %, 10%, 15%, 17.5%, 20% and 20% respectively.

Source: Tables 4.6-4.13, pp.239-246 of the resubmission.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

6.61 The total cost to PBS/RPBS over the first 6 years of listing was estimated to be \$30 to \$60 million. The key drivers of the results were darbepoetin alfa assumed uptake rates, chemotherapy utilisation rates, and proportion of non-myeloid cancer patients receiving chemotherapy who had CIA. The estimates may be under-estimated for the following reasons:

- Low rates of uptake of darbepoetin alfa assumed in the resubmission;
- Potentially higher chemotherapy utilisation rate than assumed in the resubmission and
- Varying estimates of proportion with CIA from different sources.

6.62 Cost savings to the health budget were based on the costs of transfusions (\$ per transfusion). As discussed, considerable uncertainty exists around the costs of transfusion assumed in the economic model, it is unreasonable to assume 100% of transfusions would incur the cost of a hospital admission. The net cost to the government health budget may be underestimated.

6.63 The November 2007 resubmission estimated a much higher total cost to the PBS of more than \$100 million over the first five years of listing. DUSC adjusted this down to more than \$100 million over the first five years of listing using revised patient numbers and the weighted net cost to PBS or published price; and more than \$100 million over the first five years using revised patient numbers and the effective price (7.3.DUSC.ADV.5).

6.64 DUSC considered the estimates presented in the submission to be underestimated, because:

- The proposed restriction does not exclude repeated use of darbepoetin alfa by patients with recurrence of cancer or receiving multiple lines of chemotherapy, but this was not taken into account in the estimates.

- The method used to determine the incidences of malignancies that are commonly treated with myelotoxic chemotherapy regimens may not be appropriate. DUSC considered a better approach to the estimates would be starting with the number of people supplied chemotherapy rather than the incidence of cancer.
- There is uncertainty regarding the uptake of darbepoetin alfa for CIA in practice. The uptake could potentially be low due to the time taken to see a clinical benefit in the context of short-term symptoms that often resolve when chemotherapy is completed, and safety concerns associated with darbepoetin alfa.
- There is concern regarding potential use beyond the restriction to treat mild anaemia, particularly given the clinical trial included patients with mild anaemia, or fatigue due to cancer and/or chemotherapy with normal haemoglobin levels.

Quality Use of Medicines

6.65 No quality use of medicines information was presented in the resubmission.

Financial Management – Risk Sharing Arrangements

6.66 No risk sharing arrangements were proposed in this resubmission.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the Section 100 (Highly Specialised Drugs Program) Authority Required listing of darbepoetin alfa for the treatment of moderate to severe CIA. This decision was due to an uncertain clinical need and ongoing concerns regarding overall mortality and VTE rates with darbepoetin alfa across the proposed PBS population. In addition, the PBAC considered the selective use of data and concerns regarding RBC transfusion rate and cost assumptions used in the economic model meant that the ICER was highly uncertain.
- 7.2 The PBAC noted, unlike a RBC transfusion which quickly increases a patient's Hb level, darbepoetin alfa gradually increases Hb concentration over a period of weeks. The PBAC agreed with the ESC that the delay in treatment response compared to a RBC transfusion would likely limit the use of darbepoetin alfa in clinical practice. As such, the PBAC considered it unlikely that there was a high clinical need for darbepoetin alfa in CIA.
- 7.3 The PBAC considered that the comparator of standard medical management, which includes RBC transfusions, was appropriate.
- 7.4 The PBAC considered that, consistent with previous submissions, overall the new trial evidence (Study 782, Katsumata 2009 and Suzuki 2008) presented in the resubmission supported the claim that darbepoetin alfa was superior in terms of effectiveness compared to standard medical management for Hb and transfusion outcomes. The PBAC noted that trial data provided in the resubmission did not show a significant improvement in QoL for patients treated with darbepoetin alfa. However, the PBAC

agreed with the ESC that the additional evidence presented in the PSCR on QoL outcomes for four of the included studies (Study 114, Study 291, Study 297 and Study 161) and the eAQUA observational study suggested there may be a link between Hb level and QoL.

- 7.5 The PBAC noted that the results from Study 782 in patients with NSCLC found darbepoetin alfa to be non-inferior to placebo for overall mortality and PFS. In addition, the PBAC noted that thromboembolic events occurred at a similar rate in the darbepoetin alfa and placebo arms of Study 782 (89/1685 (4.7%) versus 34/833 (4.1%)). The PBAC considered that the findings of Study 782 supported the safety of darbepoetin alfa use in patients with NSCLC when Hb < 100 g/L and treatment to a ceiling Hb of 120 g/L. However, PBAC noted that in Study 161, conducted in patients with lymphoproliferative cancers, overall mortality was significantly worse for those treated with darbepoetin alfa (HR (95%CI): 1.36 (1.02, 1.82)). The PBAC also noted that, although not specified in the darbepoetin alfa TGA indication, both the NCCN 2018 guidelines and the FDA do not recommend ESA for patients receiving myelosuppressive chemotherapy with curative intent. The PBAC was concerned that the impact of darbepoetin alfa on overall mortality may vary depending on cancer type and stage.
- 7.6 The PBAC noted that the results of pooled analyses conducted during the evaluation of AEs from included trials found thromboembolic events were significantly higher for darbepoetin alfa versus placebo (RR (95%CI): 1.44 (1.10-1.89)). The PBAC also agreed with the ESC that the broader literature on ESAs was relevant to safety considerations for darbepoetin alfa and noted the results of a Cochrane review (Tonia et al 2012) which found that the risk of VTE was increased in patient receiving ESAs (RR (95%CI): 1.52 (1.34-1.74)).
- 7.7 The PBAC agreed with the ESC that that variation in overall survival and thromboembolic events was evident across trials for different cancers and at different Hb levels. As such, the PBAC advised that the claim of non-inferior comparative safety was not adequately supported for the proposed PBS population.
- 7.8 The PBAC noted that, while a number of trials were examined in the resubmission, the only results relied on in the resubmission's modelled economic evaluation was the result for Hb response for darbepoetin alfa from the fixed dose single arm of Study 231. The PBAC considered that the selective use of Hb response for darbepoetin alfa from Study 231 meant that the model was not based on the clinical outcomes presented in the resubmission. As a result, the PBAC considered that the base case overestimated the proportion of patients who received a RBC transfusion in the standard medical management arm compared to the main trial evidence (Study 782). The PBAC noted that the RBC transfusion rate was a key driver of the model and agreed with the ESC that the impact on the model of the selective use of results from Study 231 was high and favoured darbepoetin alfa.
- 7.9 The PBAC agreed with the ESC that the cost of transfusion (\$██████████) in the modelled economic analysis, which assumed 100% inpatient management of RBC transfusions,

was unreasonably high. The PBAC noted that variation in the inpatient/outpatient split of RBC management increased the ICER from a base case showing darbepoetin alfa [REDACTED], to less than \$15,000/QALY for a 50:50 split and \$105,000/QALY to \$200,000/QALY for a 25:75 split. The PBAC did not accept the sponsors argument that a 50:50 split of inpatient/outpatient management of RBC transfusions was supported by the AIHW and MBS data presented in the PSCR or by the retrospective observational study by Gross et al 2016 provided in the pre-PBAC response as the data provided in these sources were not specific for the use of blood or blood products in CIA. The PBAC considered that the appropriate inpatient/outpatient management split for transfusions remained uncertain as did the proportion of patients who would require a new admission for a RBC transfusion.

- 7.10 The PBAC concluded that concerns regarding assumptions used to determine the cost of transfusion and the number of transfusions avoided in the economic model meant that the ICER was highly uncertain.
- 7.11 The PBAC noted the view of DUSC that the estimates of utilisation presented in the resubmission are underestimated.
- 7.12 The PBAC noted that this resubmission is eligible for Independent Review.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

The sponsor had no comment.