the standardized mean (95% CI) difference[6] in FACT-F score between erythropoiesis-stimulating agents and no treatment was 0.23 (0.10 to 0.36, $P = 0.001$).

The NCCN and EORTC treatment guidelines (**Section 4.4.3**) recommend raising hemoglobin levels to improve patient HRQoL (Bokemeyer, Aapro et al., 2004; Rodgers, 2006). In their analysis, an EORTC-endorsed independent task force identified 36 studies that provided supporting evidence that increasing hemoglobin levels with erythropoiesis-stimulating agents leads to HRQoL improvements in patients with chemotherapy-induced anemia (Bokemeyer, Aapro et al., 2004). Statistically significant improvements in HRQoL measured using a variety of validated scales were reported in each study for patients receiving erythropoiesis-stimulating agents compared with controls.

4.4 CLINICAL USE AND COMPARABILITY OF ERYTHROPOIESIS-STIMULATING AGENTS SUPPORTED BY REPORTS FROM INDEPENDENT BODIES, META-ANALYSES, AND PRACTICE GUIDELINES

Summary of Section

- AHRQ issued a report in 2006 describing their meta-analyses on the use of erythropoiesis-stimulating agents. They observed no clinically significant difference between epoetin alfa and darbepoetin alfa in hemoglobin response, reduction in transfusion requirements, and rates of thromboembolic events. (**Section 4.4.1**).
- Ross et al (2006) observed that darbepoetin alfa and epoetin alfa had comparable clinical efficacy (reductions in transfusions, hemoglobin outcomes, improved QoL) and comparable risks of thromboembolic events. No differences from control with respect to survival were noted (**Section 4.4.2.1**).
- Bohlius et al (2006) observed that patients treated with either darbepoetin alfa or epoetin alfa had a lower risk of transfusion than control patients, were more likely to achieve a hematologic response, had a higher risk of thromboembolic risk, and had similar rates of overall survival (**Section 4.4.2.2**).
- NCCN recently published in 2006 updates to their evidence-based treatment guidelines for anemia in cancer (**Section 4.4.3**).

[6] Ross et al (2006) standardized the mean differences within each study before the meta-analysis by taking the difference between studies and dividing this by the pooled standard deviation of the difference between studies.

4.4.1 Report from Agency for Healthcare Research and Quality Technology Evaluation Center Provides Evidence to Support the OPPS 2007 Draft Rule

In 2006, AHRQ released its final report, "*Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment.*" The report compares the efficiency and adverse effects of the 2 erythropoiesis-stimulating agents darbepoetin alfa and epoetin alfa and addresses questions relevant to optimizing the use of these agents as a general class. It found no clinically significant difference in effectiveness of these agents and also concluded that significant questions remain unanswered about this class.

4.4.1.1 Background

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) authorizes AHRQ to conduct systematic reviews of healthcare items and services that are important to Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has established a network of Evidence-based Practice Centers (EPCs) that now lend their expertise to AHRQ's Effective Health Care Program by conducting cost effectiveness reviews of pharmaceuticals, biologicals, devices, and other relevant interventions, including strategies for how these items and services can be best organized, managed, and delivered.

AHRQ commissioned the Blue Cross Blue Shield Technology Evaluation Center to conduct 10 systematic reviews, one of which examines the role of erythropoiesis-stimulating agents in the management of patients undergoing cancer treatment.

4.4.1.2 Key Findings of the Report

In summary, the report had the following key findings:

- There is no clinically significant difference between epoetin alfa and darbepoetin alfa in hemoglobin response.
- The 2 products were equally effective in:
    - increasing hemoglobin concentration.

- reducing the need for transfusion compared with untreated patients (30% of erythropoiesis-stimulating agent treated vs 50% of untreated)

- The 2 products had similar rates of thromboembolic events (ie, blood clotting) in those studies directly comparing the products.
- Approximately 7% of patients receiving either product experienced a thromboembolic event, compared with 4% of untreated patients.
- Some studies sought to maintain hemoglobin levels higher than recommended on product labels, but the evidence was insufficient to determine whether this increased the risk of thromboembolic events.
- Overall, quality-of-life measures tended to favor treatment with either product, but the selection of measures and reporting of results were inconsistent. Individual trial results were variable and, more importantly, the clinical significance of study results on quality of life is uncertain. The report also said that more research is needed to determine whether small improvements in quality-of-life survey scores translate into a noticeable improvement for the patient.
- Insufficient data is available to conclude survival risk or benefit. One study reported that erythropoiesis-stimulating agents might decrease survival, and another study suggested that the products might accelerate progression of some cancers; however, both of these findings remain unconfirmed. The review also identified significant research gaps where more evidence is needed, including more data delineating the effects of survival, tumor progression, and the risk of adverse events when the products are administered as currently recommended.

4.4.1.3 AHRQ Comment on Synchronization

The report stated that dosing strategies are optimally convenient when they minimize office visits (eg, every third week in patients undergoing chemotherapy cycles of three weeks each). Except for low-dose arms in some early dose-finding studies, the evidence reviewed here showed no between-arm differences in transfusion rate for any comparisons of different doses, schedules, regimens, or routes of administration.

4.4.1.4 AHRQ Critique of Waltzman and Exploratory Endpoints

One of the studies that formally compared epoetin alfa and darbepoetin alfa was the Waltzman et al (2005) study (**Section 4.1.2**). This study was planned as a superiority comparison of epoetin alfa versus darbepoetin alfa.

The AHRQ report highlighted this study in its discussion of hemoglobin response, pointing out that it was unique in observing a statistically significant difference in proportion of patients with a > 2-g/dL increase in hemoglobin from baseline by week 17 that favored epoetin over darbepoetin alfa with respect to early hemoglobin response. AHRQ pointed out that this study (Waltzman, Croot et al., 2005) adjusted dose for inadequate initial response at different times in the 2 treatment arms: patients with < 1-g/dL rise in hemoglobin had the dose increased 50% at week 6 if randomized to darbepoetin alfa (from 200 to 300 mcg every 2 weeks), but at week 4 if randomized to epoetin alfa (from 40,000 to 60,000 U/week). The report indicated that this had the potential to bias the results.

AHRQ discussed exploratory endpoints that have also been discussed in some publications on erythropoiesis-stimulating agents. The endpoint of early increase in hemoglobin (eg, 1-g/dL rise after 4 weeks) was identified by the report as not being useful in predicting responses to erythropoiesis-stimulating agents. Among the 10 studies that measured the early increase in hemoglobin (and/or equivalent hematocrit) and determined the correlation with eventual full hematologic response, data were reported in various formats without sufficient information to transform them into a common format. However, where sufficient information was available on performance characteristics, at best the results are positive predictive values of 80% to 89% and negative predictive values of 65% to 71%, which are not likely clinically useful in determining which patients should or should not continue to receive erythropoiesis-stimulating agents.

The AHRQ report, we believe, provides a wealth of evidence that supports our long held positions on the efficacy and safety of darbepoetin alfa. We also believe that this evidence clearly supports CMS's treatment of darbepoetin alfa in the proposed OPPS rule for 2007.

4.4.2 Meta-analyses Published in Peer Review Journals Generally Concur with the AHRQ Report and Provide Further Evidence to Support for the OPPS 2007 Proposed Rule

Meta-analyses based on published studies reflect a relatively high level of evidence (**Figure 3-2**). Two meta-analyses on erythropoiesis-stimulating agent use in cancer patients have been published recently (**Sections 4.4.2.1 and 4.4.2.2**). A summary of their results is provided (**Table 4-4**).

Table 4-4. Summary of Bohlius et al (2006) and Ross et al (2006) Meta-analyses

Measure	Meta-analysis Results	
	Bohlius et al (2006)	**Ross et al (2006)**
Risk for RBC transfusions	• Patients treated with darbepoetin alfa (DA) or epoetin alfa (EA) had 36% lower risk of transfusion than control patients (RR = 0.64, 95%CL: 0.60, 0.68)	• Patients treated with either agent had similar risk of transfusions compared with control: EA vs control (OR = 0.44, 95%CL: 0.35 to 0.55) and DA vs control (OR = 0.41, 0.31 to 0.55).
Hematologic response (≥ 2-g/dL rise in hemoglobin)	• DA- and EA-treated patients were more likely to achieve a hematologic response (RR = 3.43, 95%CL: 3.07, 3.84)	• Not assessed
Risk of thromboembolic events	• DA- and EA-treated patients had a 67% higher risk of a thromboembolic event than control patients (RR = 1.67, 95%CL: 1.35, 2.06)	• No difference was observed in the risk of thromboembolic events between the erythropoietic agents DA/EA and controls: OR = 1.41, 95%CL: 0.81, 2.47.
Impact on overall survival	• Impact of DA and EA treatment on overall survival remains uncertain (HR = 1.08 95%CL: 0.99, 1.18)	• No difference was observed in all-cause mortality between DA/EA compared with control (OR = 1.00, 95%CL: 0.69, 1.44)
Quality of life	• Not assessed	• Treatment with DA or EA improved QOL compared with control (mean difference in FACT-F = 0.23, 95:CI = 0.10, 0.36; *P*=0.001)

DA = darbepoetin alfa; EA = epoetin alfa; RR = relative risk; CL = confidence limits; HR = hazard ratio; QOL = quality of life; FACT-F = FACT-Fatigue

Source: (Bohlius, Wilson et al., 2006; Ross, Allen et al., 2006)

4.4.2.1 Bohlius et al (2006) - Independent

Bohlius and colleagues (2006) recently published an update to their independently sponsored systematic review of 57 trials that included 9353 patients, using publications between January 1, 1985 and April 30, 2005 as available in The Cochrane Library, MEDLINE, EMBASE, and conference proceedings.

They evaluated risk for RBC transfusions, likelihood of hematologic response, risk of thromboembolic events, and overall survival. Their findings are summarized in **Table 4-4**. The manuscript is included for your reference (**Section 7.1.1**).

4.4.2.2 Ross et al (2006) – Amgen Sponsored

Ross et al (2006) recently published the results of a meta-analysis of 40 trials that included 21,378 patients. The references included those published as full papers between 1980 and July 2005 or as abstracts from the 2003, 2004, or 2005 annual proceedings of American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), or European Society of Medical Oncology (ESMO). The databases searched included MEDLINE, Current Contents, and PubMed. The authors also looked at bibliographies from any identified recent systematic reviews in the Cochrane Library to identify additional candidate references.

They evaluated risk for RBC transfusions, risk of thromboembolic events, overall survival and quality of life (**Table 4-4**). The manuscript is included for your reference (**Section 7.1.1**).

4.4.3 Evidence-based Practice Guidelines

As described above, evidence-based medicine has become an important part of making decisions for patient care. Various independent bodies have employed evidence-based medicine approaches to develop treatment guidelines. Independent organizations like ASH, ASCO, European Organisation for Research and Treatment of Cancer (EORTC), and National Comprehensive Cancer Network (NCCN) have developed evidenced-based guidelines on the treatment of chemotherapy-induced anemia, and anemia in cancer.

Further, the prescribing information for the erythropoiesis-stimulating agents, agreed upon by regulatory bodies and pharmaceutical companies, are also based on the

evidence of a drug's safety and efficacy demonstrated in the clinical drug development program. This information helps provide guidance on appropriate treatment.

Below is a summary of the current evidence-based guidelines for the management of chemotherapy-induced anemia categorized by the guidelines' recommendations (**Table 4-5**).

Amgen has looked to these guidelines to help inform clinical trial design, using them to define target hemoglobin ranges (11 to 13 g/dL) to help define and evaluate appropriate endpoints for clinical trials (Boccia, Imtiaz et al., 2006; Canon, Vansteenkiste et al., 2006).

Table 4-5. Current Evidence-Based Guidelines for the Management of chemotherapy-induced anemia

Recommendations	US FDA[a]	EMEA[b]	ASCO/ASH[c]	EORTC[d]	NCCN[e]
Initiate erythropoietic treatment	Not specified; Hb < 11 g/dL inferred from other sections of the USPI	Hb ≤ 11 g/dL	Hb ≤ 10 g/dL (clinical decision if < 12 g/dL and > 10 g/dL)	Hb 9 to 11 g/dL	Hb < 10 g/dL (consider treatment when Hb is 10 to 11 g/dL)
Objective of treatment	To maintain Hb level 10 to 12 g/dL	To maintain Hb level between 12 and 13 g/dL	To maintain Hb level at or near 12 g/dL	To maintain Hb level between 12 and 13 g/dL	To maintain Hb level at or near 12 g/dL
Cessation of ESA treatment	If Hb exceeds 13 g/dL	In the absence of an Hb response, even after dose escalation, discontinue therapy. Stop treatment approximately 4 weeks after the end of chemotherapy.	In the absence of a Hb response, even after dose escalation, discontinue therapy after 6 to 8 weeks	In the absence of a Hb response, even after dose escalation, discontinue therapy	In the absence of a Hb response, even after dose escalation, discontinue therapy after 8 to 12 weeks
Hb target > 12 g/dL	Target Hb concentrations should not exceed 12 g/dL	Target Hb no higher than 13 g/dL	No evidence to suggest additional benefit if target Hb concentrations above 12 g/dL	Target Hb no higher than 13 g/dL	No evidence to suggest additional benefit if target Hb concentrations above 12 g/dL

Note: Hb = hemoglobin; ESA = erythropoiesis-stimulating agent

a: US Prescribing Information (USPIs) for ESAs

b: European Medical Evaluation Agency (EMEA) Summary of Product Characteristics for ESAs

c: American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) (Rizzo, Lichtin et al., 2002)

d: European Organisation for Research and Treatment of Cancer (EORTC) (Bokemeyer, Aapro et al., 2004)

e: National Comprehensive Cancer Network (NCCN) (Rodgers, 2006)

5. ECONOMIC ANALYSIS

Summary of Section
• Applying a level of evidence approach to examination of the products demonstrate that Medicare and its beneficiaries pay about the same or less for darbepoetin alfa than for epoetin alfa (**Section 5.1**). • Claims data must be interpreted with caution as these data generally cannot establish clinical benefit, only drug utilization (as billed for) (**Section 5.3**). Its susceptibility to bias and data integrity problems places these data low on the level of evidence scale, especially in contrast to randomized, controlled trials. • Average weekly doses calculated from claims data must be carefully adjusted for the established period of clinical benefit (**Section 5.3**). Failure to do this can bias results against agents with longer periods of clinical benefit.

The levels of evidence described earlier (**Section 3.2**) can be used to perform cost assessments. Examining data for consistency across these different levels can provide greater confidence in decisions made from such data.

The placement and strength of each level of evidence is generally well agreed upon, as even Ortho Biotech has stated:

> The gold standard for comparing the safety and efficacy of two products and to establish a conversion ratio is a well-designed, head-to-head controlled clinical trial. When clinical trial data are not available, alternate data sources may permit an approximation. These non-trial data sources would include drug registries, patient chart data, and medical practice data. Each of these data sources has its respective advantages and disadvantages. However, claims data sets do not represent an alternative data source to determine a conversion ratio. Claims data sets provide information only on drug dosing and lack key components to assess patient outcome.[7]

And:

> Prospective, randomized, controlled clinical trials designed and powered to directly compare hematologic outcomes represent the highest level of evidence ('the gold standard') for understanding the relative efficacy, or dose conversion ratio, of erythropoietic agents.[8]

Having established from the clinical hierarchy of evidence that darbepoetin alfa and epoetin alfa are equivalent at commonly used doses (Schwartzberg, Shiffman et al., 2003; Patton, Reeves et al., 2004; Schwartzberg, Yee et al., 2004; Glaspy, Vadhan-Raj

[7] Memorandum to CMS , J&J Methodology (July 3, 2003)

[8] Letter from Joaquin Duato, President, Ortho Biotech Products, L.P., to Mark McClellan, Administrator, Centers for Medicare & Medicaid Services (Jan. 6, 2006)

et al., 2006), other less rigorous forms of usage data (such as claims analysis) may also help inform how clinical trial data translates into drug utilization. Data from claims analysis must be interpreted with caution because in general no measure of clinical benefit is attached to the utilization data (**Section 5.3**). For this reason, claims data are an inappropriate data source to inform the discussion in the previous section on relative clinical benefit of agents.

Average weekly dose data derived from claims analysis require careful analysis, as the duration of clinical benefit (DCB) will vary between agents and depends on the dose of that agent administered to the patient. The established DCB for doses of darbepoetin alfa greater than 300 mcg is 3 weeks. Therefore, applying an inappropriately short DCB to longer-acting agents such as darbepoetin alfa will result in artificial inflation of average weekly doses. This is especially true in chemotherapy-induced anemia, where treatment periods are generally short (on the order of 12 to 16 weeks). Failing to account for the DCB in this setting can systematically bias the analysis against longer-acting therapies. In fact, Ortho Biotech has also recognized the appropriateness in DCB methodology when calculating average weekly dose in analyses submitted to CMS[9] as well as in the recent publication of the economic analysis of their head-to-head trial of darbepoetin alfa and epoetin alfa (Reed, Radeva et al., 2006).

5.1 CLINICAL TRIALS HAVE DEFINED THE DOSES OF DARBEPOETIN ALFA THAT ARE EFFICACIOUS, SAFE, AND EFFECTIVE

The evidence base defining doses of darbepoetin alfa that are efficacious is broad, as dose-finding studies and clinical develop programs by definition evaluate a range of doses. There are many clinical trials that support the efficacy and effectiveness of darbepoetin alfa (**Table 5-1**). Importantly, the darbepoetin alfa doses used in these studies are broadly comparable across dosing schedules. These are the doses that CMS should rely upon when conducting an economic analysis comparing darbepoetin alfa and epoetin alfa. For epoetin alfa, there are several studies supporting the efficacy and safety of 40,000 U QW, the most important of which was their registrational trial (Witzig, Silberstein et al., 2005), and secondarily is CMS's determination that this is the dose to which darbepoetin alfa should be compared.

[9] July 3, 2003 Methodology Briefing Document submitted to CMS.

Table 5-1. Dosing of Darbepoetin alfa Every 2 Weeks – Review of Data Previously Provided to CMS

Study/Data Source	Number of Patients	Comparable Clinical Efficacy?	Average Dose Administered	
			Darbepoetin alfa	Epoetin alfa
Randomized, Active-controlled Comparisons Between Darbepoetin alfa and Epoetin alfa				
Amgen sponsored				
(Schwartzberg, Yee et al., 2004)	312	Yes	218 mcg Q2W[1]	39,949 U QW
(Glaspy, Vadhan-Raj et al., 2006)	1,220	Yes	229 mcg Q2W[2]	42,714 U QW
Ortho sponsored				
(Waltzman, Croot et al., 2005)	358	Yes (TFN, Hb by EOS) No (1-g/dL rise in Hb in 4 wks)	205 mcg Q2W[1]	38,179 U QW
Prospective, Single-arm Community Studies				
SOAR™ (DA dose = 3 mcg/kg)				
(Vadhan-Raj, Mirtsching et al., 2003)	1,558	Yes, vs historical control[3]	251 mcg Q2W[1]	42,950 U QW[3,4]
SURPASS (DA dose = 200 mcg)				
(Gabrilove, 2004)	2,401	Yes, vs historical control[3,4]	187 mcg Q2W[1]	42,950 U QW[3,4]

1: Q2W dose is calculated by multiplying average weekly dose administered (accounting for every-2-week dosing interval) by 2.

2: Calculated as simple mean of all doses administered.

3: Gabrilove (2001) used as historical control due to similarity in study design, population and therapy duration.

4: Data from Ortho Biotech LP briefing document to CMS: 3 July 2003 (page 24).

Note: TFN = transfusions, Hb = hemoglobin; EOS = end of study; DA = darbepoetin alfa

Table 5-1. Dosing of Darbepoetin alfa Every 2 Weeks – Review of Data Previously Provided to CMS (Continued)

Study/Data Source	Number of Patients	Comparable Clinical Efficacy?	Average Dose Administered	
			Darbepoetin alfa	Epoetin alfa
Comparative Medication Use Evaluation Studies[1]				
Amgen MUE				
(Schwartzberg, Shiffman et al., 2003)	967	Yes	200 mcg Q2W[2]	34,005 U QW
CLEAR				
(Herrington, Davidson et al., 2004)	1,838	Yes	190 mcg Q2W[2]	34,164 U QW
Analysis of Administrative Databases				
Medicare 100%				
Hospital outpatient data (Moran, 2004)	19,249,280 claim lines	N/A	196 mcg per claim	40,607 U per claim
Health Plans				
Ingenix (2006) [1]	7287 EOCs	N/A	104 mcg[3] per EOC	36,637 U[3] per EOC
PharMetrics (2006) [~70]	2006 EOCs	N/A	99 mcg[3] per EOC	39,103 U[3] per EOC
MarketScan (2006) [~80]	7176 EOCs	N/A	94 mcg[3] per EOC	35,496 U[3] per EOC

1: Based on most common initial dose/schedule.

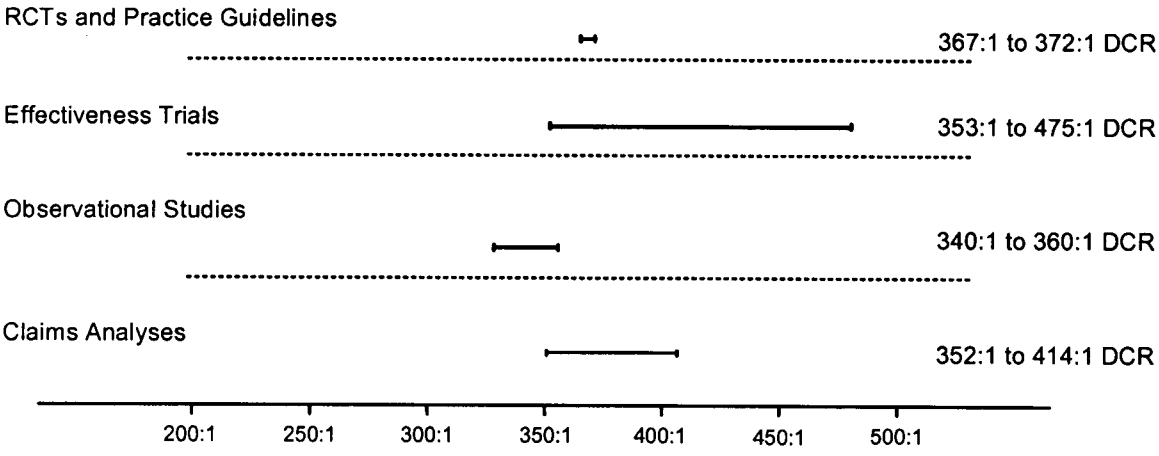
2: Q2W dose is calculated by multiplying average weekly dose administered (accounting for every 2 week dosing interval) by 2.

3: Dose calculated adjusting for duration of clinical benefit.

Note: N/A: Not applicable; EOC: episode of care = the total duration of therapy (ie, timeframe) during which a patient is receiving benefit from a treatment, including the duration of clinical benefit associated with last drug claim.

Figure 5-1 provides the range of doses observed across the range of available studies, organized according to the level of evidence discussed earlier (**Section 3.2; Figure 3-2**). This does not contend that dose conversion ratios (DCR) are an appropriate metric, but rather that they can be the basis for comparing the cost of darbepoetin alfa relative to epoetin alfa across the body of evidence.

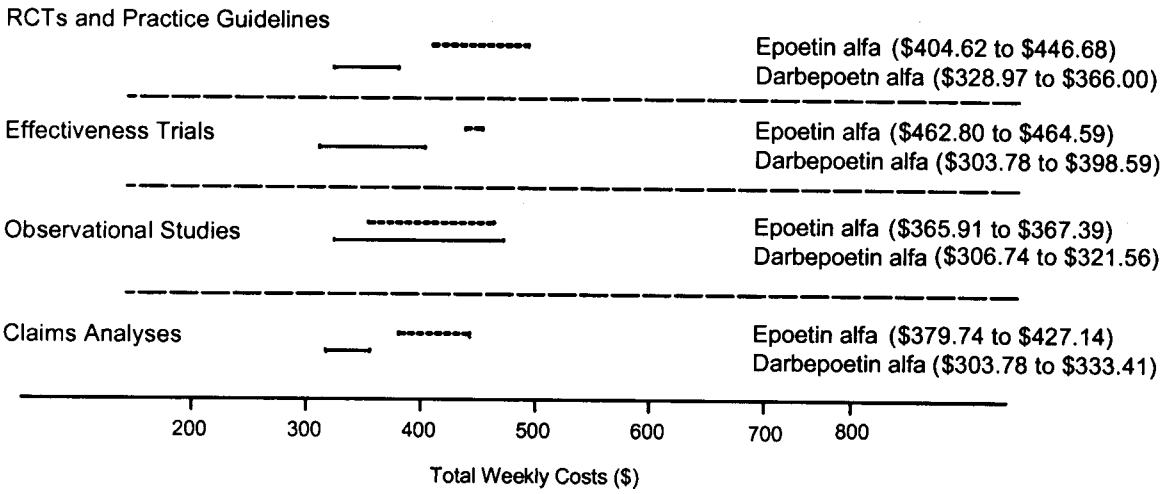
Figure 5-1. Ranges of Dose Conversion Ratios Across the Evidence Hierarchy



Notes: DCRs were calculated from most commonly used doses and do not include every dosing regimen.

When we evaluate the range of costs across the evidence hierarch, it is apparent that there are no meaningful differences in costs, even when the entire range of data is investigated (**Figure 5-2**).

Figure 5-2. Estimated Weekly Product and Service Costs Across the Evidence Hierarchy



Notes: DCRs were calculated from most commonly used doses and do not include every dosing regimen. Because actual services rendered depend on the needs of specific patients, patients may receive an administration service, an outpatient visit, either service, or some other combination of services on a particular date of service. Estimated weekly costs are DCRs from **Figure 5-1** multiplied by ASP+5 percent. ASP+5 percent payment rates are based on fourth-quarter 2006 ASP+6% published payment rates.

When evaluating the highest levels of evidence, including the RCTs that form the basis of the doses recognized in national evidence-based guidelines (Rosberg, Ben-Hamadi et al., 2005), and doses proven to be effective in community based effectiveness trials, CMS pays less for darbepoetin alfa than epoetin alfa over a wide range of potential doses. This conclusion is based on evaluating doses known to be efficacious and consistent with those shown to achieve comparable outcomes for the 2 products. Importantly, these doses are fully consistent with the most frequently administered doses observed in clinical practice using chart reviews and claims data.

When an economic analysis is based on observational studies, including both prospective registries and retrospective chart reviews, it is apparent that across the range of applicable doses, the costs to the Medicare program and its beneficiaries for darbepoetin alfa are less than or about the same as those for epoetin alfa.

Finally, we have performed an economic analysis of claims data consistent with our previous OPPS submissions to CMS. Even with conservative assumptions applied, darbepoetin alfa costs less than epoetin alfa. An analysis conducted by the Moran Company of the most recently available OPPS claims data for 2005 is presented in

Appendix B. The results from an economic analysis using the Moran data are included in **Appendix C**.

As demonstrated above, it is clear that across the body of evidence, darbepoetin alfa is less costly than epoetin alfa when measuring drug costs using doses that have demonstrated efficacy. We recognize, however, that these doses are not the doses administered at every injection due to dose titration that may occur at the individual patient level. Nonetheless, these doses are consistent with the average weekly doses we have observed, the most commonly administered doses, and the average administered doses. Medicare and its beneficiaries spend less on darbepoetin alfa than epoetin alfa for chemotherapy-induced anemia across the hierarchy of evidence. This conclusion supports CMS finalizing its proposal to base the payment for darbepoetin alfa on its own ASP and to not apply an "equitable adjustment" to darbepoetin alfa in 2007.

5.2 ORTHO BIOTECH'S ECONOMIC ANALYSIS OF ITS OWN SPONSORED STUDIES CONCLUDE THAT EPOETIN ALFA IS MORE EXPENSIVE THAN DARBEPOETIN ALFA

Reed et al (2006) published an economic analysis of the Waltzman et al (2005), comparing resource use, cost and clinical outcomes for epoetin alfa and darbepoetin alfa according to pre-specified methods. In an evaluation of total costs, based on a mean follow-up duration of 11.8 weeks, mean total cost was higher for the epoetin alfa arm than the darbepoetin alfa arm (**Table 5-2**). The main difference in cost was attributed to longer hospital stays in the epoetin alfa arm (10.6 days) than in the darbepoetin alfa arm (7.2 days), with a mean difference of 3.5 days (95% CI: 0.35 to 6.36). There were no significant differences in rate of hospitalization (mean number of hospitalizations, 0.34 vs 0.27, respectively; difference, 0.08 [95% CI: -0.05 to 0.22]). When inpatient care was removed from the analysis, a cost difference remained that favored darbepoetin alfa.

Table 5-2. Mean (SD) Costs of Epoetin alfa and Darbepoetin alfa Treatment in the Waltzman et al (2005) Study

Costs	Epoetin alfa (n = 175)	Darbepoetin alfa (n = 177)	Difference
Direct medical costs (drugs, injections, and other services)	$14,525 (9167)	$13,676 (7138)	$849 (95% CI: -866, 2530)
Indirect costs (patient time)	$451 (192)	$425 (170)	$26 (95% CI: -11, 66)
Total direct medical and indirect costs	$14,976 (9247)	$14,101 (7220)	$875 (95% CI: -849, 2607)

Note: Total costs included costs for inpatient care, blood transfusions, unplanned radiation therapy, and laboratory services, drugs (chemotherapy and non-chemotherapy), patient time, study medications and administration of study medication.

5.3 ADMINISTRATIVE CLAIMS DATA NEED TO BE USED JUDICIOUSLY AFTER CONSIDERATION OF ITS LIMITATIONS AND ACCOUNTING FOR DIFFERENCES IN DURATION OF CLINICAL BENEFIT

Summary of Section

- Equalizing clinical/demographic characteristics and addressing possible DCB differences for darbepoetin alfa and epoetin alfa can substantially change the average weekly doses calculated from claims data; unadjusted average weekly doses may be extremely misleading.
- In addition, comparisons of dose using claims data must be interpreted with caution because such data lack information on patient clinical outcomes of erythropoiesis-stimulating agent therapy and are subject to bias including data recording errors and confounding by indication.

Equalizing clinical/demographic characteristics and addressing possible DCB differences for darbepoetin alfa and epoetin alfa can substantially change the average weekly doses calculated from claims data; unadjusted average weekly doses may be extremely misleading. In addition, comparisons of dose using claims data must be interpreted with caution because such data lack information on patient clinical outcomes of erythropoiesis-stimulating agent therapy and are subject to bias including data recording errors and confounding by indication.

Administrative claims data are not intended for research but for billing and payment purposes. Such data are susceptible to bias and data-integrity problems. Estimates are highly variable and in the presence of higher levels of evidence such as randomized,

controlled trials, these data should be used to support findings from more internally valid sources or to generate hypotheses. Plus, data from claims analysis must be interpreted with caution because in general no measure of clinical benefit is attached to the utilization data. Johnson and Johnson has also recognized the limitations of claims data:

> Claims data alone lack sufficient information to support the conversion ratio determination. A clinical metric, such as hemoglobin level, is essential to calibrate the doses of each drug needed to achieve the same clinical benefit.[10]

And

> In developing the conversion ratio, CMS should take into account hematologic outcomes and not rely solely on claims data. Claims data alone are not sufficient to support a conversion ratio determination.[11]

5.3.1 Amgen Approach to the Analysis and Results

Defining DCB is a critical element when comparing products with different dosing schedules over comparable periods of time. The episode of care (EOC) is the timeframe during which a patient receives benefit from a treatment. This represents the total duration of therapy, including the DCB associated with last drug claim. **Table 5-3** illustrates the DCB for darbepoetin alfa and epoetin alfa.

Table 5-3. Durations of Clinical Benefit by Erythropoiesis-stimulating Agent and Dose Administered

	Dose	Duration of Clinical Benefit (DCB)
Darbepoetin alfa	≤100 mcg	7 days
	101 – 299 mcg	14 days
	≥ 300 mcg	21 days
Epoetin alfa	≤ 15,000 U	2 days
	15,001 – 35,000 U	5 days
	> 35,000 U	7 days

The EOCs with erythropoiesis-stimulating agent therapy were constructed based on information on paid claims using valid and imputed claims. Medical claims with

[10] Memorandum to CMS , J&J Methodology (July 3, 2003)

[11] Letter from John H. Johnson, President, Ortho Biotech Products, L.P., to Hon. Thomas A. Scully, Administrator, Centers for Medicare & Medicaid Services (Oct. 3, 2003)

questionable or potentially erroneous data were defined on the basis of: paid amounts < $50 or > $4000, billed units < 10 or > 80[12] while pharmacy claims with invalid data were defined on the basis of therapy-days equaled 0.

A DCR without adjustment for DCB does not consider the time over which the doses were administered. The DCR that results from this method can be thought of as a ratio of dose per administration (or per claim) of epoetin alfa divided by dose per administration (or per claim) of darbepoetin alfa, rather than as a ratio of weekly doses.

5.3.2 Amgen-sponsored Claims Analyses Employing DCB

Two healthcare claims database analyses were conducted to compare dosing with erythropoiesis-stimulating agents in patients with cancer receiving chemotherapy in a real-world setting.

5.3.2.1 PharMetrics Database

Berger et al (2006) conducted a recent analysis of a large US health-insurance database (~15 million covered lives), of all patients with cancer receiving erythropoiesis-stimulating agents (N = 1787) between January 2005 and June 2005. There were 1323 unique erythropoiesis-stimulating agent episodes with darbepoetin alfa, 683 unique erythropoiesis-stimulating agent episodes with epoetin alfa and 219 patients with multiple erythropoiesis-stimulating agent episodes. A copy of the presentation is provided for your reference (**Section 7.1.4**, (Berger, Kallich et al., 2006)). The manuscript is currently in preparation.

First, they calculated the length of erythropoiesis-stimulating agent episodes, applying EOC and DCB methodology to account for differences in the respective serum half-lives:[13]

[12] Prior to January 1, 2006: one Healthcare Common Procedure Coding System (HCPCS) unit was defined as 1,000 U for Epoetin alfa and 5 mcg for darbepoetin alfa. Pharmacy claims with invalid data defined on basis of: Therapy-days = 0.

[13] The length of erythropoiesis-stimulating agent episodes was calculated based on date of last erythropoiesis-stimulating agent administration plus estimated days of benefit (based on quantity of darbepoetin alfa or epoetin alfa dispensed) minus date of first erythropoiesis-stimulating agent administration. The duration of clinical benefit was derived in part from recommendations on dosing set forth in package inserts for epoetin alfa (Ortho Biotech Products, 2005) and darbepoetin alfa (Amgen Inc., 2006), as well from recently published studies that have compared these 2 agents in people with chemotherapy-related anemia (Glaspy et al, 2006; Waltzman et al, 2006; Schwartzberg et al, 2004; Mirtsching et al, 2002).

- Darbepoetin alfa: 7 days if the final dose of was ≤100 mcg, 14 days if the final dose was 101 to 299 mcg, and 21 days for all other doses
- Epoetin alfa: 7 days if the final dose (ie, within the EOC) was ≥35,000 U, and 2 days for all other doses.

Second, they performed a sensitivity analysis, changing the DCB assigned to the final claim for erythropoiesis-stimulating agent therapy within an EOC from that reported above to:

- Darbepoetin alfa: If claim was for <60 mcg, add 2 days; if claim was for 60 mcg to 149 mcg, add 7 days; if claim was for 150 mcg to 299 mcg, add 14 days; if claim was for ≥300 mcg, add 21 days;
- Epoetin alfa: If claim was for ≤15,000 U, add 2 days; if claim was for 15,001 U to 35,000 U, add 5 days; if claim was for >35,000 U, add 7 days;

Mean weekly dose was calculated based on length of erythropoiesis-stimulating agent episode and total dose of erythropoiesis-stimulating agent dispensed.

There were differences in the demographic and clinical characteristics of darbepoetin alfa and epoetin alfa patients. Patients receiving darbepoetin alfa were more likely to be women, suffering from breast cancer, and younger than those receiving epoetin alfa (P <0.05). Results from the analyses are presented in **Table 5-4**.

Table 5-4. Overview of Results from Berger et al (2006)

	Epoetin alfa EOCs (N=683)	Darbepoetin alfa EOCs (N=1,323)	*P*-Value
Number of claims included in analyses	3,847	4,967	
Mean dose per claim (95% CI)	44,503 (43,711, 45,293)	209 (206, 212)	
Mean weekly dose during EOC (95% CI)	42,634 (40,492, 44,928)	99 (96, 102)	
Mean number of administrations per EOC (SD)	5.6 (5.8)	3.8 (3.2)	
Median* days between doses	7	14	
Number of EOCs	683	1,323	
Number of EOCs with >1 administrations of ESA therapy (%)**	516 (75.5)	945 (71.4)	
Mean duration of EOC (SD) (days)	51.3 (51.3)	54.8 (43.7)	<0.001
Number of EOCs with one of the following (%)*			
1 ESA administration only	167 (24.5)	378 (28.6)	
QW dosing	157 (23.0)	36 (2.7)	
Q2W dosing	248 (36.3)	387 (29.3)	
Q3W dosing	65 (9.5)	365 (27.6)	
Other	46 (6.7)	157 (11.9)	
Number of EOCs by tumor type (%)*			
Breast cancer	182 (26.6)	448 (33.9)	
Lung cancer	88 (12.9)	163 (12.3)	0.011
NHL	60 (8.8)	100 (7.6)	
Other cancer	353 (51.7)	612 (46.3)	
Mean weekly (SD) cost for ESA therapy during EOCs, $	667 (559)	571 (307)	0.012

* Median is reported because these data are highly variable and skewed, making median a better summary statistic and representation of the clinical practice

**Total number of EOCs used as denominator

Note: Doses of EA expressed in Us;doses of DA expressed in mcgs; EA: Erythropoietin alfa; DA: Darbepoetin alfa; EOC: Episode of care; ESA: Erythropoietin-stimulating agent; QW: Once weekly; Q2W: Once every 2 weeks; Q3W: Once every 3 weeks; NHL: Non-Hodgkin's lymphoma

Table 5-5 shows that whichever DCB is used the weekly costs are equivalent for the 2 drugs and that the DCR (epoetin alfa:darbepoetin alfa) is between 383.4 and 427.9.

Table 5-5. Berger et al (2006) Analysis of PharMetrics Claims Data: Doses and Costs Associated with Application of EOC and DCB Methodology

	Darbepoetin alfa	Epoetin alfa
First Approach[1]		
Dose, Mean (SD)	99 (52.1) mcg	42,634 (29,970) U
Estimated Mean Weekly Reimbursed Cost	$571	$667
	Comparison of cost, P = 0.012	
Second Approach[2]		
Dose, Mean (SD)	102 (51.2) mcg	39,103 (26,643) U
Estimated Mean Weekly Reimbursed Cost	$664	$626

[1] Added DCB to the last dose delivered

[2] Estimated DCB for the last dose delivered

In univariate analyses, we estimated the dose ratio (epoetin alfa: darbepoetin alfa) to be 432:1 (ie, each mcg of darbepoetin alfa is comparable to 432 U of epoetin alfa). This ratio is consistent with prior reports of the doses at which darbepoetin alfa and epoetin alfa are customarily used in clinical practice, and with the ratio used in randomized, controlled clinical trials comparing the 2 agents (Schwartzberg, Yee et al., 2004; Waltzman, Croot et al., 2005; Glaspy, Vadhan-Raj et al., 2006). In multivariate analyses, controlling for differences between patients who receive these agents, the ratio was somewhat less (ie, 398:1).

These results suggest that comparisons of the cost of darbepoetin alfa and epoetin alfa therapy in patients with chemotherapy-induced anemia should be based on methods that account for differences in the serum half-lives of the 2 products. Comparisons of use are highly sensitive to the assumed DCB associated with the final dose of erythropoiesis-stimulating agent therapy. This study suggests that the DCR of epoetin alfa:darbepoetin alfa in clinical practice is approximately 400:1.

5.3.2.2 Medstat Database

A second analysis by Thompson Medstat employed MEDSTAT's MarketScan Commercial Claims and Encounter Database (Commercial) and Medicare Supplemental and Coordination of Benefits (COB) Database (Medicare). This has been submitted to

the American Society of Hematology for presentation in December 2006. The abstract is currently embargoed but should be published soon (Song, Long et al., 2006).

This database includes information from more than 50 large employers, with healthcare coverage[14] provided by more than 80 health plans, representing the treatment experiences of more than 14 million covered lives. The study population for this analysis consisted of patients continuously enrolled between January 2005 and June 2005 who met certain criteria.[15] Episodes of care were analyzed in a fashion similar to that described previously.[16]

First, they calculated the length of erythropoiesis-stimulating agent episodes, applying EOC and DCB methodology to account for differences in the respective serum half-lives:

- Darbepoetin alfa: 7 days (≤ 100 mcg), 14 days (101 to 299 mcg), or 21 days (≥ 300 mcg)
- Epoetin alfa: 2 days (< 35,000 IU) or 7 days (≥ 35,000 U).

Second, they performed a sensitivity analysis, changing the DCB assigned to the final claim for erythropoiesis-stimulating agent therapy within an EOC from that reported above to below:

- Darbepoetin alfa: 2 days (< 60 mcg); 7 days (60 to 149 mcg); 14 days (150 to 299 mcg); 21 days (≥300 mcg) and for
- Epoetin alfa: 2 days (≤15,000 U); 5 days (15,001 to 35,000 U); 7 days (>35,000 U).

The results of the analysis indicated that 2,574 epoetin alfa episodes of care and 2,942 darbepoetin alfa episodes of care met inclusion/exclusion criteria in January to June 2005 MarketScan database. The logistic regression results indicated that darbepoetin

[14] Healthcare for these covered lives is provided to these individuals under a variety of fee-for-service (FFS), fully capitated, and partially capitated health plans, including preferred provider organizations, point of service plans, indemnity plans, and health maintenance organizations.

[15] (1) at least 2 cancer claims or 1 claim for chemotherapy or radiation between December 2004 and June 2005; (2) at least one claim for an erythropoiesis-stimulating agent between January 2005 and June 2005; and (3) no evidence of renal disease. A panel data set consisting of records that represented erythropoiesis-stimulating agent episodes of care were constructed for the study population

[16] Episodes of care for each patient represented services delivered from the time period between the first erythropoiesis-stimulating agent administered in the January 2005 and June 2005 time period and the last erythropoiesis-stimulating agent administered or a 42 or more day gap in erythropoiesis-stimulating agent therapy. Episodes were dropped from the study where: 1) the patient was not continuously enrolled January to June 2005; 2) had both darbepoetin alfa and epoetin alfa use; or 3) had one or more claims with missing or invalid doses that could not be imputed.

alfa EOCs were more likely in patients that were younger, had higher Charlson Comorbidity Index scores, had more advanced cancer, and had been treated with chemotherapy or radiation than those receiving epoetin alfa EOCs (**Table 5-6**). Song et al (2006) also found that patients with a single administration of an erythropoiesis-stimulating agent are 77% more likely to use darbepoetin alfa than epoetin alfa.

Table 5-6. Overview of Results for Song et al (2006): Treatment Patterns for Erythropoiesis-stimulating Agents, by Type of Episode of Care (Epoetin alfa vs. Darbepoetin alfa)

Parameter	Epoetin alfa	Darbepoetin alfa	p-value
Weekly dose, mean [SD]	44,044 (37,327)	94.2 (48.4)	NA
Number of days between consecutive administrations			
Mean (SD)	11.7 (7.7)	15.7 (7.0)	<0.0001
Mode (median)*	6 (8.5)	13 (13)	NA
Number of administrations			
1, n (%)	823 (32.0)	1036 (40.2)	<0.0001
2-5, n (%)	1,094 (42.5)	1543 (59.9)	
≥6, n (%)	657 (25.5)	363 (14.1)	
Mean (SD)	4.0 (±3.8)	2.9 (±2.4)	<0.0001
Duration of therapy, in days			
<30, n (%)	1,423 (55.2)	1,418 (55.1)	<0.0001
30-59, n (%)	517 (20.1)	746 (29.0)	
60-89, n (%)	305 (11.8)	446 (17.3)	
≥90, n (%)	327 (12.7)	332 (12.9)	
Mean (SD), days	37.7 (±36.3)	43.2 (±32.6)	<0.0001
Evidence of NDC claims, %	449 (17.4)	105 (4.1)	<0.0001
Dose conversion ratio** (Epoetin alfa:darbepoetin alfa)	468		

* Median and mode are reported because these data are highly variable and skewed, making these summary statistics a better representation of the clinical practice

** This does not contend that DCRs are an appropriate metric, but rather that they can be the basis for comparing the cost of darbepoetin alfa relative to epoetin alfa across the body of evidence.

SD = standard deviation

The DCB analysis revealed that epoetin alfa was more sensitive to DCB changes than darbepoetin alfa. Switching from the first approach to the second increased average weekly dose for darbepoetin alfa from 94 mcg to 105 mcg, while epoetin alfa average weekly dose decreased from 44,044 U to 35,496 U. When an ANOVA adjustment is

performed to adjust for differences in the populations, estimated average weekly dose for the first approach and the second, respectively, were 97 mcg and 104 mcg for darbepoetin alfa and 41,902 U and 34,973 U for epoetin alfa.

5.3.2.3 Conclusions for Claims Analyses

Equalizing clinical/demographic characteristics and addressing possible DCB differences for darbepoetin alfa and epoetin alfa can substantially change the average weekly doses calculated from claims data; unadjusted average weekly doses may be extremely misleading. In addition, comparisons of dose using claims data must be interpreted with caution because such data lack information on patient clinical outcomes of erythropoiesis-stimulating agent therapy and are subject to bias including data recording errors and confounding by indication.

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7. ATTACHMENTS

7.1 ATTACHMENT: LIST OF REFERENCES PROVIDED AS PART OF SUBMISSION

7.1.1 Data from Head-to-head Trials

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7.1.2 Data Supporting Darbepoetin alfa Administered Q3W

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7.1.3 Data from Meta-analyses

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7.1.4 Data from Claims Analyses

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7.2 ATTACHMENT: QUESTIONS CONCERNING SURVIVAL IN PATIENTS TREATED WITH ERYTHROPOIESIS-STIMULATING AGENTS REMAIN UNANSWERED

Summary of Section

- Some concerns have been expressed concerning survival risk in patients receiving erythropoiesis-stimulating agents based on nonclinical data (**Section 7.2.1**) and clinical data as discussed in **Section 7.2.2**.
- To date, however, clinical study data (**Section 7.2.2**) and the assessments of independent bodies (**Section 7.2.3**) suggest there is no survival risk in treating patients with chemotherapy-induced anemia with erythropoiesis-stimulating agents.
- Pending analysis of upcoming studies that are actually powered to evaluate survival, the question about survival risks associated with erythropoiesis-stimulating agents remains unanswered.

In both the medical and the regulatory communities, there has been significant interest in survival rates associated with erythropoiesis-stimulating agent use. To date, no study has reported that was prospectively designed to specifically evaluate survival.

7.2.1 Nonclinical Data

Erythropoietin primarily triggers responses by acting on erythropoietin receptors that are present on cell surfaces. One concern regarding survival and erythropoiesis-stimulating agents lies in observations that some tumor cells appear to express erythropoietin receptors, raising the possibility that tumor growth may be stimulated if these agents stimulate these receptors (for example, (Acs, Xu et al., 2004; Arcasoy, Amin et al., 2005; Arcasoy, Amin et al., 2005; Dagnon, Pacary et al., 2005)). Recently published evidence, however, raises some doubt as to whether these cells actually express erythropoietin receptors because the antibodies used to detect the erythropoietin receptor in tumor cells may not be as specific to erythropoietin receptors as originally thought (Elliott, Busse et al., 2006). Further, these receptors have to be on the cell surface in order for erythropoietin to stimulate them. These antibody experiments to date have measured the total amount of erythropoietin receptors in cells, not just those expressed on the cell surface of cells. Some cells, like tumor cells, may make erythropoietin receptors, but may not actually express them on the cell surface, making them effectively inactive. Additional experiments have found virtually no expression of these receptors on the cell surface of tumor cells (Sinclair, Busse et al., 2005). Therefore, the actual risk associated

with erythropoiesis-stimulating agents and potential stimulation of tumor growth remains uncertain.

7.2.2 Clinical Data

Limited clinical data are available from randomized clinical trials addressing survival in cancer patients who received erythropoiesis-stimulating agents, and no completed studies have been designed with adequate statistical power to determine survival benefit.

Concerns regarding the potential adverse effect of erythropoiesis-stimulating agents on survival were in part triggered by the first publications of 2 trials, Henke et al (2003) and Leyland-Jones (2003). Both studies allowed hemoglobin values to increase to levels higher than those recommended by treatment guidelines. The Henke trial, which evaluated epoetin beta, has been criticized for the high number of protocol deviations, but concludes this does not explain the adverse results. However, there are also concerns regarding important imbalances in baseline factors (such as smoking), the heterogeneous nature of the populations studied, which may not have been adequately stratified to account for inherent survival differences, and the results of the prespecified per-protocol analysis, which showed no evidence of adverse outcomes for the epoetin beta group. Similar criticisms can be applied to the design and conduct of the Leyland-Jones trial. In fact, the final publication of Leyland-Jones et al study (2005) subsequently confirmed the data presented at the FDA ODAC meeting that there was no difference in time to progression between placebo and epoetin-treated patients.

No detrimental effects on survival have been observed in randomized, controlled trials involving darbepoetin alfa, and the safety profile of darbepoetin alfa is well established. These studies, however, were not designed to evaluate survival as a primary endpoint. Recently, a comprehensive review of available data found that that there was no significant difference in survival outcome noted between patients receiving placebo and those receiving darbepoetin alfa (Hedenus, Vansteenkiste et al., 2005). We have collected long-term, follow-up, progression-free survival data from an additional double-blind, placebo-controlled trial and have conducted an analysis of progression-free survival on data pooled from the following double-blind, placebo-controlled trials (**Table 7-1**). These analyses revealed no differences in progression-free survival between darbepoetin alfa and placebo.

Table 7-1. Progression-free Survival in Darbepoetin alfa Studies

Study	Reference	Tumor Type	Median FUP (months)	Median (95% CI) Progression-free Survival	
				Darbepoetin alfa	Placebo
A	Vansteenkiste et al (2002)	Lung cancer	15.8	5.1 months (4.1 to 6.9) (n = 155)	4.4 months (3.7 to 5.3) (n = 159)
B	Hedenus et al (2003)	LPM	32.6	14.2 months (12.2 to 17.5) (n = 175)	15.9 months (13.1 to 19.0) (n = 169)

LPM = lymphoproliferative malignancies; FUP = follow-up period
Source: (Hedenus, Vansteenkiste et al., 2005)

Several ongoing randomized, controlled trials are prospectively examining the question of survival in this patient population, and the findings of those studies will shed more light on this question. Amgen has developed a robust pharmacovigilance program, including 5 randomized, prospective clinical trials, to more formally and prospectively address survival and disease progression endpoints in patients receiving darbepoetin alfa (**Table 7-2**). These trials will allow a prospectively planned evaluation of the survival question.

Table 7-2. Randomized, Prospective Clinical Trials to Address Survival and Disease Progression Endpoints in Patients Receiving Darbepoetin alfa Therapy

Sponsor/ Investigator	Tumor Type	Design (Chemotherapy Regimen)	Accrual through July 2006 (actual/target enrolled)
GELA/ R. Delarue, A. Bosley	NHL	R-CHOP 14 or R-CHOP 21 with or without darbepoetin alfa	130/600
AGO/M. Untch	Neo-adjuvant Breast	Sequential or dose- intensified chemotherapy with or without darbepoetin alfa	720/720
WSG/U.Nitz	Adjuvant Breast	Adjuvant chemotherapy with or without darbepoetin alfa	472/1000
DAHANCA/ J. Overgaard	Head/ Neck	Radiotherapy with or without darbepoetin alfa	469/600
Amgen	SCLC	Cisplatin / carboplatin/VP16 with or without darbepoetin alfa	600/600

Note: NHL = nonHodgkin's Lymphoma, SCLC = small-cell lung cancer

7.2.3 Independent Bodies and Meta-analyses

Recently, the FDA reviewed in detail the available evidence on survival, tumor progression, and thromboembolic events using patient-level data (US Food and Drug Administration, 2004). Other regulatory agencies and guideline committees have taken similar approaches. The findings from all of these authoritative bodies have been highly consistent and confirm the positive risk-benefit profile of erythropoiesis-stimulating agent therapy when used to achieve hemoglobin concentrations within the approved range (11 to 13 g/dL). The conclusion of the FDA's investigation of these results (including an ODAC meeting) was a change in labeling for all erythropoiesis-stimulating agents marketed in the US that states:

> Two additional studies explored the effect on survival and/or disease progression following administrations of two other ESPs (ie, epoetin alfa and epoetin beta) with higher hemoglobin targets. The first study was a randomized controlled study in 939 women with metastatic breast cancer receiving chemotherapy where patients received either weekly epoetin alfa or placebo for up to a year. This study was designed to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit of 36% to 42%). Mortality at 12 months was significantly higher in the epoetin alfa arm. This difference was observed primarily in the first 4 months of the study with more deaths attributed to breast cancer progression in the epoetin alfa group (6% epoetin alfa vs. 3% placebo). Due to insufficient monitoring and data collection, reliable comparisons cannot be made concerning the effect of epoetin alfa on overall time to disease progression, progression-free survival, and overall survival. The second study was a randomized controlled study in 351 head and neck cancer patients where epoetin beta or placebo was administered to achieve target hemoglobins of 14 and 15 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter (median of 406 days epoetin beta vs 745 days placebo, P = 0.04) in patients receiving epoetin beta.
>
> There is insufficient information to establish whether use of epoetin ESP products, including Aranesp® darbepoetin alfa, have an adverse effect on time to tumor progression or progression-free survival. These studies permitted or required dosing to achieve a hemoglobin level greater than 12 g/dL. Until further information is available, the recommended target hemoglobin, as contained in the Aranesp® package insert, should not exceed 12 g/dL in men or women.
>
> – (Amgen Inc., 2006)

The recent AHRQ report (Seidenfeld, Piper et al., 2006) concluded that there was insufficient evidence to conclude survival risk or benefit (**Section 4.4.1**). The report pointed out that one study reported that erythropoiesis-stimulating agents may decrease

survival, and another study suggested that the products might accelerate progression of some cancers; however, both of these findings remain uncertain. Ross et al (2006), in a meta-analysis (funded by Amgen) performed in parallel and partially in response to that done by AHRQ, observed no differences in mortality rates between erythropoiesis-stimulating agents and control (**Section 4.4.2.2**).

Bohlius et al (2006) in their meta-analysis of 57 trials, indicated that the impact of erythropoiesis-stimulating agent therapy on survival is currently neutral (hazard ratio = 1.08, 95%CL: 0.99, 1.18) (**Section 4.4.2.1**).

7.3 ATTACHMENT: CURRENT DATA ON THROMBOEMBOLIC EVENTS

Summary of Section
• There is evidence that patients with cancer may be predisposed to thromboembolic events (**Section 7.3.1**). • Multiple studies suggest there is a greater increase in thromboembolic event risk in patients receiving erythropoiesis-stimulating agents than in those who do not (**Sections 7.3.2 and 7.3.3**).

For erythropoiesis-stimulating agents, a specific subset of adverse events has been of particular interest to regulators, ie, thromboembolic adverse events. This interest arises from the theoretical risk of these events related to increasing RBC counts.

7.3.1 Risk of Thromboembolic Events in Patients with Cancer

An increased risk of thromboembolic events has been observed in patients with cancer and in those treated with erythropoiesis-stimulating agents. Numerous studies have addressed the relationship between thrombosis and cancer (Hillen, 2000; Otten, Mathijssen et al., 2004). Factors thought to contribute to the risk of thromboembolic events include cancer type and stage, age, immobility, and type of therapeutic interventions (chemotherapy, hormonal therapy, and radiation therapy) (Bevilacqua, Pober et al., 1986; Falanga and Donati, 2001; Kakkar, Levine et al., 2003). Hypercoagulable states, direct injury to the vascular endothelium, and inflammation may all predispose patients with cancer to thromboembolic events (Bevilacqua, Pober et al., 1986; Falanga and Donati, 2001; Kakkar, Levine et al., 2003). Studies of patients with cancer undergoing surgery have shown that the incidence of deep vein thrombosis was considerably higher in patients with malignant disorders than in patients with non-

malignant diseases (Sue-Ling, Johnston et al., 1986; Hillen, 2000). These observations have been confirmed in post-mortem studies in which a significantly higher incidence (30%) of thromboembolic events compared with individuals without cancer has been seen (Kakkar and Williamson, 1999). Data suggest that after the disease itself, thromboembolic events are historically the most common cause of death in patients with cancer (Ambrus, Ambrus et al., 1975; Otten, Mathijssen et al., 2004).

7.3.2 Clinical Data for Darbepoetin alfa

Risk of thromboembolic events in patients treated with darbepoetin alfa was evaluated using data from 11 studies, including all clinical development darbepoetin alfa oncology chemotherapy studies as of November 2003 (Amgen Inc., 2004). These studies included placebo- and non-placebo-controlled trials. All patients who received at least one dose of study drug were included. A total of 2,251 patients was evaluated. Overall, 6.1% of patients receiving darbepoetin alfa and 3.4% of patients receiving placebo reported thromboembolic events. Patients in the darbepoetin alfa group had a higher risk of any thromboembolic event compared with patients in the placebo group. Univariate and Cox regression analysis revealed 3 factors (darbepoetin alfa treatment, prior thromboembolic event history, and poor Eastern Cooperative Oncology Group [ECOG] performance status) to be significant predictors of thromboembolic events. Sex, age, prior cardiovascular events, race, obesity, baseline hemoglobin, dose schedule, baseline platelet counts, platinum chemotherapy, and baseline serum erythropoietin concentration were not statistically associated with thromboembolic event risk.

7.3.3 Independent Bodies and Meta-analyses

Similarly, AHRQ in their 2006 report (Seidenfeld, Piper et al., 2006) discussed thromboembolic events (**Section 4.4.1**). While rates varied widely, pooled results showed approximately 7% of patients treated with either product experienced a thromboembolic event, compared with 4% of untreated patients. They observed that studies directly comparing epoetin alfa and darbepoetin alfa showed no statistically significant difference in the rates of thromboembolic events. AHRQ also observed that some studies sought to maintain hemoglobin levels higher than recommended on product labels, but the evidence was insufficient to determine whether this increased the risk of thromboembolic events.

Two large meta-analyses of erythropoiesis-stimulating agent therapy in cancer patients had different observations as to the risk of thromboembolic event with erythropoiesis-stimulating agent therapy (**Section 4.4.2**). Ross et al (2006) observed no difference between erythropoiesis-stimulating agent therapy and no treatment. Bohlius et al (2006), part of the Cochrane analysis, observed that erythropoiesis-stimulating agent treatment increased the risk of thromboembolic event (relative risk = 1.67, 95%CL: 1.35, 2.06). The latter observation is consistent with the darbepoetin alfa prescribing information.