112

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October 6, 2006

Mark B. McClellan, MD, PhD
Administrator
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Room 445-G
Hubert H. Humphrey Building
200 Independence Avenue, SW
Washington, DC 20201

Re: CMS-1506-P; Medicare Program; Hospital Outpatient Prospective Payment System and Calendar Year 2007 Payment Rates; Proposed Rule; OPPS: Proposed Payment for Drugs, Biologicals, and Radiopharmaceuticals

Dear Administrator McClellan:

Amgen appreciates the opportunity to provide additional clinical and economic details in response to the calendar year (CY) 2007 Medicare hospital outpatient prospective payment system (OPPS) proposed rule (Proposed Rule), which the Centers for Medicare and Medicaid Services (CMS) published in the Federal Register on August 23, 2006.[1] As a science-based, patient-driven company committed to using science and innovation to dramatically improve people's lives, Amgen is vitally interested in improving access to innovative drugs and biologicals (collectively referred to in this letter as "drugs" following the agency's convention) for Medicare beneficiaries. For this reason, we provide information on the "Proposed Payment for Drugs, Biologicals, and Radiopharmaceuticals" section of the Proposed Rule as it applies to all separately payable drugs and to our innovative biological product, Aranesp® (darbepoetin alfa), in particular.[2]

As we articulated in our first submission on the proposed rule, submitted September 8, 2006, Amgen commends the agency on its proposal to use a free market-based approach to set the OPPS payment rates for separately payable drugs, including Aranesp®. The proposed average sales price (ASP) based payment methodology for separately payable drugs allows the payment rates for these products to reflect market dynamics and encourages the desired market adaptations that manufacturers and hospitals make to

1 71 Fed. Reg. 409506-49977.

2 Aranesp® is indicated for the treatment of chemotherapy-induced anemia in patients with non-myeloid malignancies and for the treatment of anemia associated with chronic renal failure, including patients either on dialysis or not on dialysis.

remain competitive. Regarding Aranesp® in particular, we are pleased that CMS continues to apply its market-based approach and does not propose to change its current position on an "equitable adjustment" to the payment rate for Aranesp®. We encourage the agency to finalize the proposal to continue using the ASP methodology to establish the 2007 OPPS payment rates for Aranesp®.

Amgen views the opportunity to respond to proposed rules such as CMS-1506-P as an important part of ensuring access to innovative drugs and biologicals for Medicare beneficiaries. Of course, this opportunity is meaningful only if the agency's proposed rule is complete with regard to issues that affect access to drugs and biologicals. Indeed, Congress recently amended the Medicare statute to ensure that proposed rules such as this identify issues that will appear in the final rule. Specifically, in the Medicare Modernization Act of 2003, Congress added section 1871(a) (4) of the Social Security Act to mandate that any provision in a final rule that is not a logical outgrowth of a previously published proposed or interim final rule must be treated as a proposed regulation and cannot take effect until there is an opportunity to comment and publication of a final rule.[3] In this context, then, a provision in the final OPPS rule that is not a logical outgrowth of the proposed rule would not go into effect on January 1, 2007, the expected effective date of the CY 2007 OPPS final rule.

In previous submissions to the agency, we have demonstrated the clinical efficacy and safety of Aranesp® and comparable outcomes to epoetin alfa across a broad range of doses. Glaspy et al. (2006) is the most definitive study on the comparability between Aranesp® dosed at 200 mcg once-every-two weeks (Q2W) and Procrit® dosed at 40,000 units (IU) once-a-week (QW).

The AHRQ report also examined the Ortho Biotech sponsored study (Waltzman et al. 2005) and its serious methodological limitations which did not attempt to assess clinical comparability between the products, and employed an unvalidated endpoint of questionable clinical validity. The validity of this endpoint had been in question prior to the AHRQ report, as demonstrated by FDA's issuance of a *Violative Advertising and Promotional Labeling Letter to Procrit®* resulting from Ortho Biotech's characterization of the study in its promotional material.[4]

This year's submission focuses on additional clinical and economic evidence that continues to provide evidence to support CMS's current policy for market-based pricing for Aranesp® for 2006, as well as the proposal to continue paying for all drugs and biologicals at an average sales price (ASP)-based methodology.

Below, we highlight key clinical and economic evidence that provides CMS with additional justification for finalizing the market-based payment rate for Aranesp® in 2007. A more detailed discussion of each of these findings is included in **Appendix A**.

- **The synchronization of anemia management with chemotherapy is beneficial to patients.** In **Section 3.1**, we highlight that synchronization of anemia management benefits patients, something that we believe strongly benefits patients and providers alike and is a direct benefit from the recent change in the

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[3] P.L. 108-173

[4] FDA (2003). *Violative Advertising and Promotional Labeling Letter for Procrit®*, http://www.fda.gov/cder/biologics/adpromo/epoamg062003.htm.

Aranesp® label – a topic thoroughly discussed in **Section 4.2**. Synchronizing anemia management with chemotherapy treatment reduces the number of needle sticks patients must receive and should result in a decrease in patient trips to the doctor.

- **It is important that the level of evidence support clinical decision making.** Clinical evidence is held to an internationally agreed set of standards. Policy makers should rely on these standards and value high quality, internally valid data over less rigorous data when making coverage decisions. In **Section 3.2**, we discuss how the strongest types of analyses within the hierarchy of evidence provide support for CMS' proposed 2007 OPPS payment rate for Aranesp®.

- **Aranesp® has demonstrated efficacy and safety when administered every-three-weeks, allowing flexible and synchronized dosing with chemotherapy.** In **Section 4.2**, we discuss the recent FDA approval and benefits to patients and providers of the addition of every-3-week dosing to the label for Aranesp®.

- **Treating cancer patients' anemia has been demonstrated to improve quality of life.** The evidence has strengthened for quality of life improvements in cancer patients with chemotherapy-induced anemia treated with erythropoiesis-stimulating agents continues to grow (**Section 4.3**).

- **There have been important new advances in addressing questions about erythropoiesis-stimulating agents in the past year.** The Agency for Healthcare Research and Quality (AHRQ) published a report in 2006 on the comparability in efficacy and safety of darbepoetin alfa to epoetin alfa. The AHRQ report is consistent with the evidence that supports CMS's policy decisions for Aranesp® in the proposed rule. Data from multiple updated meta-analyses on erythropoiesis-stimulating agents have also been published including the Bohlius et al (2006) publication and the Ross et al (2006) publication (**Section 4.4**). These analyses continue to add to the evidence base that provides support for our long held positions regarding Aranesp® and the clinical comparability of the 2 products and provides evidence to support the agency's proposed OPPS payment methodology for most drugs and biologicals for 2007.

- **Aranesp® costs about the same or less than Procrit®. Section 5.1** updates the economic analyses of Aranesp® and Procrit® demonstrating that Aranesp® consistently costs Medicare and beneficiaries the same or less than Procrit® at commonly administered doses – a theme consistent with our previous submissions. In fact, Ortho-Biotech's own sponsored economic analysis of the Waltzman trial found darbepoetin alfa to be less costly overall than epoetin alfa (**Section 5.2**).[5] Of note is the finding that over the course of treatment in the Waltzman trial, Procrit® cost on average $875 more per patient than Aranesp®.

To be consistent with our research findings from previous years, we also provide an update on the current data available on survival (**Section 7.2**) and thrombotic events (**Section 7.3**) in patients treated with erythropoiesis-stimulating agents. In light on the

[5] Reed S, Radeva J, Daniel D, et al.. "Economic evaluation of weekly epoetin alfa versus biweekly darbepoetin alfa for chemotherapy-induced anaemia: Evidence from a 16-week randomised trial." Pharmacoeconomics: 24(5): 479-494.

clearly demonstrated lower or comparable costs of Aranesp®, CMS should finalize the proposed payment rate for the product.

In summary, Amgen agrees with the agency's proposed payment for Aranesp® and the use of market-based pricing to reimburse for separately payable outpatient drugs.

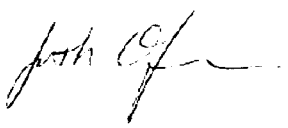
As CMS prepares to finalize changes to OPPS for 2007, we recommend the following:

- Maintain market-based treatment of Aranesp® in order to achieve significant Medicare payment reductions and savings for beneficiaries, and
- Continue to use the market-based ASP percent methodology to set payment rates for separately payable outpatient drugs.

* * * * *

Amgen appreciates this opportunity to provide important information and looks forward to working with you to ensure that Medicare beneficiaries treated in the hospital outpatient setting continue to have access to new and important biological therapies. Please contact Sarah Wells Kocsis by phone at (202) 585-9713 or by email at **wellss@amgen.com** to arrange a meeting or if you have any questions regarding our response. Thank you for your attention to this important matter.

Regards,



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AMGEN

Appendix A

The Clinical and Economic Outcomes with Darbepoetin alfa (Aranesp®)

October 6, 2006

Confidentiality Statement

Because the enclosed documents contain confidential commercial and trade secret information, they are exempt from disclosure under the Freedom of Information Act (FOIA). If CMS receives a FOIA request for these documents, we ask that you contact Amgen and allow us to assist you in identifying and redacting the confidential portions of these documents before their release.

1. TABLE OF CONTENTS

2. ABBREVIATIONS

Abbreviation	Definition
AHRQ	Agency for Healthcare Research and Quality
ANOVA	Analysis of variance
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ASP	Average sales price
CI	Confidence interval
CL	Confidence limits
CMS	Centers for Medicare and Medicaid Services
COB	Coordination of benefits
DA	Darbepoetin alfa
DCB	Duration of clinical benefit
DCR	Dose conversion ratio
EA	Epoetin alfa
EMEA	European Medical Evaluation Agency
EOC	Episode of care
EORTC	European Organisation for Research and Treatment of Cancer
EOTP	End of the treatment period
EPC	Evidence-based Practice Center
FACT-An	Functional Assessment of Cancer Therapy – Anemia subscale
FACT-F	Functional Assessment of Cancer Therapy – Fatigue subscale
FDA	Federal Drug Administration
FFS	Fee for service
HCPCS	Healthcare Common Procedure Coding System
Hematopoietic response	≥ 2-g/dL rise in hemoglobin or achieving hemoglobin ≥ 12 g/dL
Hemoglobin response	≥ 2-g/dL rise in hemoglobin from baseline
HRQoL	Health-related quality of life
ICD-9	International Classification of Diseases, 9th edition
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Abbreviation	Definition
LVCF	Last value carried forward
mcg	Microgram
MMA	Medicare Prescription Drug Modernization Act of 2003
NCCN	National Comprehensive Cancer Network
N/A	Not applicable
NR	Not reported
OBI	Ortho-Biotech Inc.
OPPS	Outpatient Payment and Policy System
OR	Odds ratio
PSQ-An	Patient satisfaction questionnaire for anemia treatment
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QW	Weekly
RBC	Red blood cell
RCT	Randomized, controlled clinical trial
SCHIP	State Children's Health Insurance Program
SD	Standard deviation
USPI	US Prescribing Information

3. EXECUTIVE SUMMARY

In this document, Amgen highlights key clinical and economic evidence that provides the Centers for Medicare and Medicaid Services (CMS) with additional justification for finalizing the market-based payment rate for Aranesp® (darbepoetin alfa) in 2007. The proposed methodology under the Medicare hospital outpatient prospective payment system (OPPS) for reimbursing all separately payable drugs and biologicals allows market dynamics to truly determine the appropriate payment for drugs and biologicals. For 2006, CMS finalized their proposal to not apply an "equitable adjustment" to darbepoetin alfa and in the proposed rule for 2007, makes no mention of such an "equitable adjustment" for any drug or biological, nor solicits any comment on the issue.

In previous submissions to the agency, we have demonstrated the clinical efficacy and safety of Aranesp® and comparable outcomes to epoetin alfa across a broad range of doses. Glaspy et al. (2006) is the most definitive study on the comparability between Aranesp® dosed at 200 mcg once-every-two weeks (Q2W) and Procrit® dosed at 40,000 units (IU) once-a-week (QW).

The AHRQ report also examined the Ortho Biotech sponsored study (Waltzman et al. 2005) and its serious methodological limitations which did not attempt to assess clinical comparability between the products, and employed an unvalidated endpoint of questionable clinical validity. The validity of this endpoint had been in question prior to the AHRQ report, as demonstrated by FDA's issuance of a Violative Advertising and Promotional Labeling Letter to Procrit® resulting from Ortho Biotech's characterization of the study in its promotional materials.[1]

This year's submission focuses on additional clinical and economic evidence that continues to provide evidence to support CMS's current policy for market-based pricing for darbepoetin alfa for 2006, as well as their proposal to continue paying for all drugs and biologicals using an average sales price (ASP)-based methodology.

Key highlights include:

- In **Section 3.1**, we highlight that synchronization of anemia management with chemotherapy strongly benefits patients and providers alike and directly arises

[1] FDA (2003). *Violative Advertising and Promotional Labeling Letter for Procrit®*, http://www.fda.gov/cder/biologics/adpromo/epoamg062003.htm.

out of our recent change in the darbepoetin alfa label – a topic thoroughly discussed in **Section 4.1**.

- It is important that be supported by the highest level of evidence (**Section 3.2**) and that it is these strongest and well-validated data that support CMS's decision regarding payments for separately payable drugs under OPPS.
- Darbepoetin alfa was approved for every-3-week dosing by the US Food and Drug Administration (FDA) (**Section 4.2**).
- The evidence for quality of life improvements in cancer patients with chemotherapy-induced anemia treated with erythropoiesis-stimulating agents continues to grow (**Section 4.3**).
- Data from multiple updated meta-analyses on erythropoiesis-stimulating agents have also been published, including the Agency for Healthcare Research and Quality (AHRQ) report, the Bohlius et al (2006) publication, and the Ross et al (2006) publication (**Section 4.4**). These analyses continue to add to the evidence base that supports our long held positions regarding darbepoetin alfa and the clinical comparability of darbepoetin alfa and epoetin alfa.
- Our recent updates to the economic analyses of darbepoetin alfa and epoetin alfa demonstrate that darbepoetin alfa consistently costs Medicare and beneficiaries the same or less than epoetin alfa – a theme consistent with our previous submissions (**Section 5.1**). In fact, Ortho-Biotech's own sponsored economic analysis of the Waltzman trial (2005) found darbepoetin alfa to be less costly overall than epoetin alfa (**Section 5.2**).
- To be consistent with our research findings from previous years, we also provide an update on the current data available on survival (**Section 7.2**) and thrombotic events (**Section 7.3**) in patients treated with erythropoiesis-stimulating agents.

As CMS prepares to finalize changes to OPPS for 2007, we recommend that the agency continue to maintain market-based treatment of darbepoetin in order to achieve significant Medicare payment reductions and savings to beneficiaries. The clinical and economic findings have long provided the evidence to support our position as we present throughout this document and referenced appendices.

3.1 SYNCHRONIZATION OF ANEMIA TREATMENT WITH CHEMOTHERAPY CAN REDUCE TREATMENT BURDEN

Summary of Section
• Anemia remains a common and debilitating complication of chemotherapy. • Chemotherapy regimens are frequently administered at intervals greater than QW, eg, 49% of chemotherapy is administered Q3W. • QW administration of erythropoiesis-stimulating agents often requires extra visits for patients not receiving QW chemotherapy. • Each visit to the doctor represents a burden on patients, caregivers, and the healthcare system • The ability to dose darbepoetin alfa at a range of frequencies, QW, Q2W and Q3W, allows synchronization of treatment for anemia with chemotherapy and could help minimize this treatment burden.

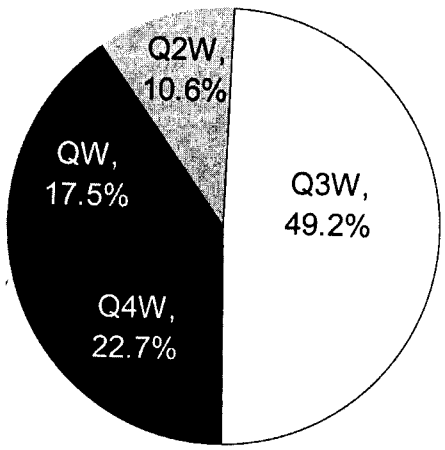
Over the past 2 decades, the advent of new chemotherapy regimens, including optimized dosing and schedules, has led to meaningful extensions of life and improvements in cancer survival (Jemal, Siegel et al., 2006). Conceptually, the doses and frequencies of myelosuppressive chemotherapy are balanced to provide maximal therapeutic benefit while minimizing risks, eg, reduction of relative dose intensity (Kwak, Halpern et al., 1990; Lepage, Gisselbrecht et al., 1993; Bonadonna, Valagussa et al., 1995). Unfortunately such treatment regimens can indiscriminately target healthy, normal cells in addition to their intended targets, leading to clinical consequences such as low red blood cell (RBC) count (ie, anemia) and/or low white blood cell count (ie, neutropenia), both of which can restrict the on-schedule administration of chemotherapy. Indeed, the pioneering work of Amgen in developing effective treatments for anemia and neutropenia has been an important factor in allowing the majority of chemotherapy to be safely and effectively administered in an outpatient setting.

Anemia and its sequelae (eg, fatigue and increased risk of requiring blood transfusions) are common in patients undergoing chemotherapy and can potentially delay or prevent subsequent administration of curative treatment. Further, anemia can result in significant reductions in patient quality of life (Cella, 1998; Groopman and Itri, 1999; Sabbatini, 2000), which is as important as length of life to many patients. Hence, agents that stimulate the production of red blood cells (ie, erythropoiesis-stimulating agents) can play an important role in modulating the toxicity of chemotherapy, especially when one considers the inherent risks associated with transfusions, including iron overload and

disease transmission (Mercadante, Gebbia et al., 2000; Stainsby, Cohen et al., 2003; Goodnough, 2005; Bohlius, Wilson et al., 2006).

Chemotherapy regimens are administered at a range of dosing frequencies, weekly (QW) to every 4 weeks (Q4W) (**Figure 3-1**).

Figure 3-1. Distribution of Chemotherapy Regimen by Dosing Frequency



Note: Frequency of top cancer therapies in selected cancer patients (N = 5,486) treated between 01Jan2003 to 08Jul2004. Adapted from GEMS-IT Version 0406. Output:: */epi/projects/epidemiology/p04_004_jdk/reports/tables/q3w/t_01_chemo_all_20060412.rtf (Date Generated: 13Apri06 (05:13))*

In the US, erythropoiesis-stimulating agents approved to treat anemia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy include:

- Epoetin alfa (Procrit®), which can be dosed 150 IU/kg three-times a week or 40,000 U QW (Ortho Biotech Products, 2005), and
- Darbepoetin alfa (Aranesp®), which can be dosed 2.25 mcg/kg QW and now 500 mcg every 3 weeks (Q3W) per the prescribing information (Amgen Inc., 2006)
    - Dosing darbepoetin alfa at 3 to 5 mcg/kg Q2W is supported by compendia listings, extensive clinical studies, and recently published additional data (Glaspy, Vadhan-Raj et al., 2006)
    - Data supporting dosing at 300 mcg Q3W was recently presented (Taylor, Ganly et al., 2005)

With darbepoetin alfa administration intervals including QW, Q2W, and Q3W, it means that over 75% of chemotherapy patients can now receive darbepoetin alfa treatment in

the same visit, rather than having to come back for anemia treatment at later visits (**Figure 3-1**). Before the availability of dosing darbepoetin alfa Q3W, just over 28% of patients could have synchronization of their chemotherapy and erythropoiesis-stimulating agent administration if one considers both Q2W and QW dosing regimens (**Figure 3-1**).

While all QW dosing of an erythropoiesis-stimulating agent can be dosed synchronously with any chemotherapy regimen, many additional clinic visits may be required solely for the purpose of anemia treatment, as both darbepoetin alfa and epoetin alfa must be administered by a healthcare provider. Darbepoetin alfa, however, can be administered less frequently. Benefits associated with less-frequent dosing regimens have been described (Beveridge, Rifkin et al., 2003; Houts, Loh et al., 2006). Clearly, these regimens require fewer injections be given to patients; compared with QW dosing, Q2W dosing requires half the number of injections, and Q3W, two-thirds fewer. In clinical practice, substitution of a more-frequently administered agent with a less-frequently administered one has reduced the number of injections given (Beveridge, Rifkin et al., 2003). Further, as blood tests are generally performed before administration of erythropoiesis-stimulating agents, fewer injections also mean that fewer blood draws are required. Fewer injections, fewer office visits, and fewer blood draws can represent a cost savings in addition to being less burdensome to patients. The use of darbepoetin alfa over epoetin alfa to treat chemotherapy induced anemia translates to direct savings to the Medicare program and its beneficiaries; a factor that positively supports CMS's decision to base the payment rate for darbepoetin alfa on its own market-based ASP. Also, less-frequently administered agents generally required a smaller time commitment from patients (Houts, Loh et al., 2006).

3.2 IT IS IMPORTANT TO CONSIDER LEVEL OF EVIDENCE TO SUPPORT DECISIONS RELATED TO CLINICAL CARE

Summary of Section
• Clinical evidence is graded according to an internationally agreed scale and should be weighted accordingly • High quality, internally valid data should be used preferentially over less valid data in making policy decisions • Internal validity is a prerequisite for external validity.

The practice of medicine involves an ever-evolving understanding as to what comprises best practice with respect to patient care, based on both practical experience and clinical research. The Institute of Medicine has defined evidence-based medicine as the conscientious and judicious use of the current, best evidence from clinical care research in the management of patients (Institute of Medicine, 2006).

This evidence is categorized according to a framework that is weighted, at least in part, according to the source of the evidence, eg, whether it arose from a randomized, controlled, comparative, double-blind trial; an open-label, single-arm clinical trial; or from a single case. This framework assumes that the highest levels of evidence have the highest degree of internal validity. The concept of internal validity consists of 2 main aspects within the study: how the variables examined in a study are measured, controlled, or manipulated and how well the study design and conduct eliminate confounding variables.

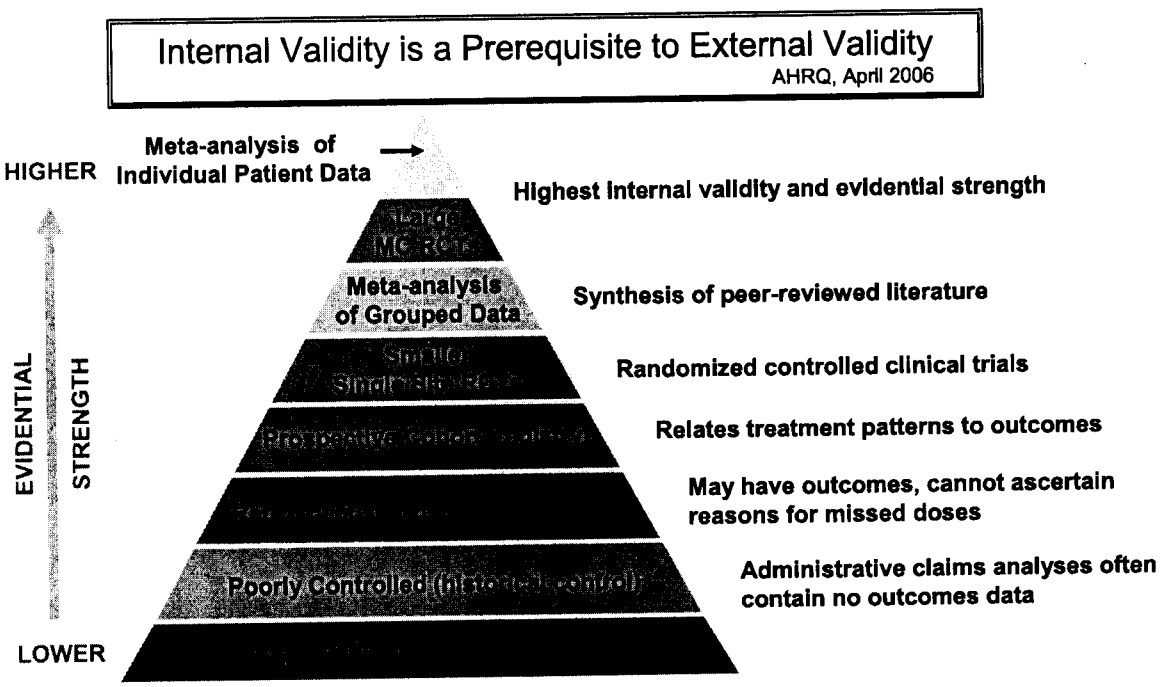
A wide range of organizations have adopted evidence-based medicine approaches in their decision-making processes. These organizations (**Table 3-1**) include those that set policy for the licensing, coverage and payment of medical technology and medical specialty societies that produce guidelines for care. In the US, these authoritative bodies include the FDA (United States Food and Drug Administration), CMS, and the Agency for Health Care Research and Quality (AHRQ).

Table 3-1. List of Authoritative Bodies

Body	Name and Description
ABIM	American Board of Internal Medicine (http://www.abim.org/) – the US board that sets the standards and certifies the knowledge, skills and attitudes of physicians who practice in Internal Medicine, its subspecialties and areas of added qualifications.
ACP	American College of Physicians (http://www.acponline.org/) – Internal medicine
AHRQ	Agency for Healthcare Research and Quality (http://www.ahrq.gov/) –charged with improving the quality, safety, efficiency, and effectiveness of health care for all Americans by promoting evidence-based decision-making.
CCOHTA	Canadian Coordinating Office for Health Technology Assessment (http://www.ccohta.ca/entry_e.html) – primary source for unbiased, evidence-based information on drugs, devices, health care systems and best practices for Canada, funded by Canadian federal, provincial and territorial governments.
Cochrane Collaboration	The Cochrane Collaboration (http://www.cochrane.org/index0.htm) – an international non-profit and independent organization that produces and disseminates systematic reviews of healthcare interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions.
CMS	Centers for Medicaid & Medicare Services (http://www.cms.gov)
NCCN	National Comprehensive Cancer Network (http://www.nccn.org) – NCCN is a not-for-profit alliance of 20 of the world's leading cancer centers dedicated to improving the quality and effectiveness of care provided to patients with cancer.
NICE	National Institute for Health and Clinical Excellence (http://www.nice.org.uk/) – the independent organization responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.
PBAC	Pharmaceutical Benefits Advisory Committee (http://www.health.gov.au/internet/wcms/Publishing.nsf/Content/health-pbs-general-outcomes.htm) – an organization that helps to decide whether and, if so, how medicines should be subsidized in Australia.
FDA	United States Food and Drug Administration (http://www.fda.gov) – responsible for assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, food supply, cosmetics, and products that emit radiation.
EMEA	European Agency for the Evaluation of Medicinal Products (http://www.emea.eu.int/) – body of the European Union that coordinates the evaluation and supervision of medicinal products throughout the European Union.
EORTC	European Organisation for Research and Treatment of Cancer (http://www.eortc.be/) – an organization that develops, conducts, coordinates, and stimulates laboratory and clinical research in Europe to improve the management of cancer and related problems by increasing survival but also patients' quality of life.

Both individual researchers and various organizations, including those that set policy for licensing, coverage and payment of medical technology, and medical specialty societies that produce guidelines for care have worked to refine their hierarchy of evidence. One attributed to CMS has been presented (**Figure 3-2**).

Figure 3-2. Level of Evidentiary Strength as Expressed by the Centers for Medicare & Medicaid Services



Source: Adapted from Presentation by Tunis S (2003) from Centers for Medicare & Medicaid Services. Medicare and New Medical Technology: 2003.

Independent researchers in clinical trial design and quality of clinical trials have also recommended a hierarchy of evidence for use when looking at different types of studies, especially for use in meta-analyses (**Table 3-2**) (Olkin, 1995; Piantadosi, 1995).

Table 3-2. Hierarchy of Evidence by Study Type

Types of Studies
1. Meta-analysis with original data**
2. Randomized control trials with meta-analyses*
3. Simple randomized control trials*
4. Series with historical controls*
5. Case control series*
6. Computer database analysis*
7. Case series with literature controls*
8. Uncontrolled case series*
9. Case reports*

**(Olkin, 1995), * (Piantadosi, 1995)
Note: Studies are listed in descending order of the level of evidence that they support.

These levels of evidence are important to consider in the decision-making process because they help provide appropriate balance in the interpretation of available data. High-quality clinical data should be weighted more heavily than less robust data such as claims analyses.

In the key determination of clinical comparability between darbepoetin alfa and epoetin alfa, clinical trial data are the most robust and appropriate source of data. The following sections present a wealth of trial data supporting, both directly and indirectly, the comparability of clinical outcomes of darbepoetin alfa administered QW, Q2W and Q3W with epoetin alfa administered QW.

In contrast some researchers argue that only real-world data should be used when evaluating the economics of drug therapies rather than data from randomized, controlled clinical trials (RCTs). To this end, real-world data can come in many forms (eg, chart reviews, registries, and claims) each with different levels of internal validity. Although some may claim external validity for such data based on its size (eg, having a million patients) or its content (eg, inclusion of paid claims), these data and the analyses based on them must have internal validity for them to have external validity.

With respect to administrative- claims data, one form of real-world data, their validity can be compromised by a few factors. First, claims data were not intended primarily for research but rather for the adjudication and payment of healthcare claims. Second, analyses of administrative claims data are subject to various forms of selection bias

(inability to adequately account for differences in patient or provider clinical and demographic characteristics, confounding by indication), data recording and processing errors (inaccurate coding/misdiagnoses, missing data, etc), the absence of clinical or patient-reported outcomes, and the inability to assess benefits accrued to providers, practices, patients or caregivers.

A landmark paper by the former chief medical officer of CMS (Tunis, Stryer et al., 2003) describes the optimal methods for using evidence for decision-making, calling for the utilization of Practical Clinical Trials (prospective comparisons) because:

> ...observational and other nonexperimental methods may not provide sufficiently robust information regarding the comparative effectiveness of clinical interventions, primarily because of their high susceptibility to selection bias and confounding...[2]

Further, Johnson and Johnson have 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.[3]

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.[4]

Therefore, because of inherent limitations in the dataset, claims analyses cannot reliably inform decisions on clinical outcome. However, **Section 5.3** demonstrates that critical analysis of such data reveals that drug utilization of erythropoiesis-stimulating agents is broadly similar to that observed in clinical trials.

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[2] Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. Journal of the American Medical Association. 2003;290(12): 1624-32.

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

[4] 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)

4. DARBEPOETIN ALFA CLINICAL UPDATE – QW, Q2W, AND Q3W DOSING

Summary of Section
• Clinical comparability of outcomes with darbepoetin alfa and epoetin alfa are supported by the final published results from multiple head-to-head trials (**Section 4.1**).
• Darbepoetin alfa was approved for Q3W dosing by the US FDA (**Section 4.1**). Data supporting this dosing regimen suggest comparable outcomes and drug utilization.
• Evidence supporting effects of erythropoiesis-stimulating agent effects on quality of life continues to grow (**Section 4.3**).
• Important new information from independent bodies, meta-analyses, and guidelines has been published, which also support comparability (**Section 4.4**).

The body of clinical knowledge for erythropoiesis-stimulating agents has undergone significant change in the past year. There have been important advances in addressing both product-specific and class-specific questions. What is clear is that these developments continue to strengthen the arguments that we believe provide the evidence to support the decisions that CMS has made in the Final 2006 and the Proposed 2007 OPPS rules in its treatment of darbepoetin alfa.

1. Final data addressing the clinical comparability of darbepoetin alfa and epoetin alfa based on head-to-head comparisons in clinical trials have been published (**Section 4.1**).

2. Darbepoetin alfa was approved by the FDA for Q3W dosing (**Section 4.1**) based largely on the results of a phase 3 study demonstrating the comparable efficacy of dosing darbepoetin alfa at 500 mcg Q3W or at 2.25 mcg/kg QW (Canon, Vansteenkiste et al., 2006). Additional data supporting 300 mcg Q3W dosing with darbepoetin alfa has been published (Glaspy, Henry et al., 2005; Taylor, Ganly et al., 2005; Boccia, Imtiaz et al., 2006). An economic analysis based on the trial dosing concludes that Medicare and its beneficiaries still pay about the same or less for darbepoetin alfa than for epoetin alfa at commonly administered doses.

3. The evidence for quality of life improvements in patients with chemotherapy-induced anemia treated with erythropoiesis-stimulating agents continues to grow (**Section 4.3**).

4. Data from multiple updated meta-analyses on erythropoiesis-stimulating agents have also been published. First, AHRQ has published its 2006 report on these agents, documenting its findings in response to the task set to it by CMS (Seidenfeld, Piper et al., 2006). Second, an update to the Cochrane analysis of erythropoiesis-stimulating agents has been published (Bohlius, Wilson et al., 2006). Lastly, an Amgen-sponsored meta-analysis of use of erythropoiesis-stimulating agents to treat chemotherapy-induced anemia has been published (Ross, Allen et al., 2006). Further, the National Comprehensive Cancer Network (NCCN) has issued an update to its guideline on treating cancer- and treatment-related anemia (Rodgers, 2006). Below we summarize these publications for your reference (**Section 4.4**).

4.1 FINAL RESULTS SUPPORTING THE COMPARABILITY OF DARBEPOETIN ALFA 200 MCG Q2W AND EPOETIN ALFA 40,000 U QW HAS BEEN PUBLISHED

Summary of Section
• Data from the head-to-head trials of darbepoetin alfa and epoetin alfa continue to support the comparability of darbepoetin alfa administered 200 mcg Q2W and epoetin alfa administered 40,000 U QW.

As described previously to CMS, Amgen conducted the largest head-to-head trial comparing darbepoetin alfa 200 mcg Q2W and epoetin alfa 40,000 U QW in over 1200 patients with nonmyeloid malignancies receiving chemotherapy. This study employed a noninferiority study design and evaluated commonly accepted endpoints. Final results of this trial have now been published in a peer-reviewed journal (Glaspy, Vadhan-Raj et al., 2006). The manuscript is provided for your reference (**Section 7.1.1**). Some of these results have been described previously to CMS.

This study met its primary objective of demonstrating noninferiority in transfusion incidence from week 5 to end of treatment period (EOTP) between the 2 treatment groups. Based on Kaplan-Meier estimates, 21% of the darbepoetin alfa group and 16% of the epoetin alfa group received blood transfusions. The upper limit of the 95% confidence interval (CI) for the difference in transfusion rates was below the prespecified noninferiority margin of 10.8%. The comparability of the 2 treatment groups was confirmed in a series of sensitivity analyses of both the primary (week 5 to EOTP) and secondary (week 1 to EOTP) transfusion endpoints, which yielded results consistent with

the primary analysis. The assessments of hemoglobin endpoints and quality of life also indicated comparable efficacy of the 2 agents. The frequency of cardiovascular/thromboembolic events was 6% for darbepoetin alfa patients and 7% for epoetin alfa patients; safety (adverse event) profiles were comparable. The data demonstrate the comparable efficacy of darbepoetin alfa Q2W and epoetin alfa QW at the administered doses.

4.1.1 The Results from Glaspy et al (2006) Are Consistent with Those Described Previously for These Dosing Regimens

Previously we have published results from 3 identical randomized, prospective, open-label, head-to-head trials of darbepoetin alfa 200 mcg Q2W and epoetin alfa 40,000 U QW for chemotherapy-induced anemia conducted concurrently in patients with breast, lung, or gynecologic malignancies (Schwartzberg, Yee et al., 2004). Data from these studies were analyzed both individually and in a combined analysis prespecified in each protocol. In summary, data from 312 patients randomized to either darbepoetin alfa 200 mcg Q2W or epoetin alfa 40,000 U QW showed no differences in the rate of transfusions, change in hemoglobin from baseline, the proportion of patients achieving either a hematopoietic response or achieving target hemoglobin, the time to achieve target hemoglobin, or the safety profile (Schwartzberg, Yee et al., 2004). An additional manuscript describing the results for the breast cancer patients alone has been published (Senecal, Yee et al., 2005) and is provided for your reference (**Section 7.1.1**).

4.1.2 Results for the Glaspy et al (2006) Study Are Generally Consistent with Those of the Waltzman et al (2005) Study Sponsored by Ortho Biotech

The Waltzman et al (2005) study was an open-label, randomized, controlled clinical study of 358 patients with chemotherapy-induced anemia using the same doses as Glaspy et al (2006). It was designed to demonstrate the superiority of epoetin alfa versus darbepoetin alfa with respect to early hemoglobin responses. No differences between the treatment arms have been reported for the accepted clinical endpoints of the proportion of patients receiving blood transfusions or for quality of life. The study, however, has several fundamental flaws that must be considered in the interpretation of the results.

- The Waltzman study employs an unvalidated endpoint as its primary endpoint (1-g/dL hemoglobin rise after 4 weeks) that is not recognized by the scientific

community, clinical experts (eg, AHRQ [**Section 4.4.1.4**]), or the FDA. This approach was also in direct contrast to the approach recommended for drug comparisons by the International Conference on Harmonisation [ICH] of Technical Requirements for Registration of Pharmaceuticals for Human Use E9 Guideline (1998).

- Examining superiority using an open-label study has the potential to systematically introduce bias in favor of epoetin alfa in comparison to darbepoetin alfa.
- Different dosing rules were applied for each product with respect to hemoglobin-driven changes in doses.
- The widespread distribution of interim analyses, both planned and unplanned, before completion of the study again raises the potential of introducing bias in an open-label study.

Subsequently, Reed et al (2006) published an economic analysis of Waltzman et al (2005), comparing resource use, cost and clinical outcomes for epoetin alfa and darbepoetin alfa according to pre-specified methods (see **Section 5.2** for more information). The study, sponsored by Ortho Biotech, found Procrit® to be a more expensive treatment than Aranesp®, providing further evidence to support the treatment of darbepoetin alfa in the proposed OPPS rule for 2007.

4.2 DARBEPOETIN ALFA HAS DEMONSTRATED EFFICACY WHEN ADMINISTERED EVERY 3 WEEKS, ALLOWING FLEXIBLE AND SYNCHRONIZED DOSING WITH CHEMOTHERAPY

Summary of Section
• Darbepoetin alfa was approved for Q3W dosing by the US FDA (**Section 4.2.1**).
• Studies evaluating darbepoetin alfa 300 mcg and 500 mcg Q3W dosing regimens have demonstrated efficacy in patients with nonmyeloid malignancies with chemotherapy-induced anemia (**Section 4.2.1**).
• Clinical outcomes with darbepoetin alfa Q3W are comparable to those seen with QW and Q2W dosing with darbepoetin alfa in previous studies
• Drug utilization in QW, Q2W and Q3W arms of darbepoetin alfa trials has been remarkably consistent, driven by appropriate dose reduction/escalation to achieve and maintain target hemoglobin.

Over 75% of patients receive chemotherapy either every 1, 2, or 3 weeks (**Figure 3-1**). As described to CMS previously, darbepoetin alfa has demonstrated efficacy when

administered QW or Q2W. Until recently, patients receiving chemotherapy Q3W have had to receive QW administration of darbepoetin alfa to treat their chemotherapy-induced anemia, which affects nearly 50% of the patient population receiving chemotherapy. The self-evident burden on patients and payers of additional clinic visits solely for the administration of anemia treatment suggests even less-frequent dosing of darbepoetin alfa could be beneficial.

Several studies are now published that provide evidence supporting the evidence of darbepoetin alfa when administered Q3W. In March 2006, the US FDA approved an additional dosing regimen for darbepoetin alfa in the treatment of chemotherapy-induced anemia: 500 mcg Q3W (Amgen Inc., 2006). With this new regimen as well as the existing QW labeled regimen and the body of evidence support Q2W dosing, there is now the ability to administer darbepoetin alfa synchronized with most chemotherapy regimens, without the need for additional visits expressly for the purpose of anemia treatment. Benefits associated with less-frequent dosing regimens have been described (Beveridge, Rifkin et al., 2003; Houts, Loh et al., 2006).

4.2.1 Darbepoetin alfa Can Be Effectively and Safely Administered Every 3 Weeks at a Dose of 500 mcg

Several studies have evaluated Q3W dosing for darbepoetin alfa, using fixed or weight-based doses. The recent US label change was largely based on the Canon et al (2006) study, which is described below (**Section 4.2.1.1**). Other studies have also examined this dosing frequency (**Section 4.2.1.2**).

4.2.1.1 Canon et al (2006) Demonstrates the Comparability of Darbepoetin alfa 500 mcg Q3W and Darbepoetin alfa 2.25 mcg/kg QW

This randomized, double-blind, double-dummy, active-controlled phase 3 trial evaluated the efficacy and safety of darbepoetin alfa administered either 500 mcg Q3W or 2.25 mcg/kg QW in 705 enrolled, adult patients with nonmyeloid malignancy and anemia (hemoglobin < 11 g/dL) who were scheduled to undergo at least 12 weeks of chemotherapy (Canon, Vansteenkiste et al., 2006). Patients were randomized 1:1 to the 2 dosing groups.

The primary endpoint to demonstrate non-inferiority was based on RBC transfusion incidence from week 5 to EOTP. Results for the primary endpoint indicated that, of the

672 patients remaining on the study at the beginning of week 5, 23% of the Q3W arm versus 30% of the QW arm (difference = -6.8%; 95% CI: -13.6% to 0.1%, adjusted) were transfused. Noninferiority was confirmed for the primary transfusion endpoint, ie, the upper limit of the 95% CI for the difference in RBC transfusions between groups of 0.1% in the unadjusted analysis did not exceed a prespecified margin of 12.5% based on previous placebo-controlled studies (Vansteenkiste, Pirker et al., 2002; Hedenus, Adriansson et al., 2003). Similar results were obtained for various sensitivity analyses, including an analysis of transfusions during the entire study period. Based on these results, the 2 dosing regimens, darbepoetin alfa 2.25 mcg/kg QW and darbepoetin alfa 500 mcg Q3W, were found to be comparable. Analysis of an exploratory endpoint of the percentage of patients achieving target hemoglobin (11 to 13 g/dL) indicated that 84% of patients receiving darbepoetin alfa Q3W and 77% of patients receiving darbepoetin alfa QW achieved target hemoglobin concentrations. The manuscript is included for your reference (**Section 7.1.1**).

Average weekly doses in this study were 125.2 mcg/week (ie, a dose of 375.6 mcg administered every 3 weeks) for the Q3W arm and 107.8 mcg/week for the QW arm, driven by the fact that nearly 75% of patients were dose reduced (initially to 300 mcg Q3W or 1.35 mcg/kg QW) as hemoglobin levels approached target.

4.2.1.2 Results from Additional Studies Support Every-3-week Dosing for Darbepoetin alfa

Other studies have also evaluated Q3W dosing of darbepoetin alfa, evaluating both fixed and weight-based dosing.

Boccia et al (2006) recently published final results from a 1493-patient, 16-week, single-arm, open-label study designed to assess the effectiveness of darbepoetin alfa 300 mcg Q3W in achieving and maintaining a target hemoglobin (11 to 13 g/dL). Nearly 80% of patients achieved the target hemoglobin concentration, with 18% of patients requiring an RBC transfusion from week 5 to end of the study and 55% achieving a clinically significant improvement in Functional Assessment of Cancer Therapy-Fatigue (FACT-F) score by the end of the study. The manuscript is included for your reference (**Section 7.1.1**). Average weekly dose in this study was 105.4 mcg/week (ie, a dose of 323.6 mcg administered every 3 weeks).

In December 2005, final results of another registrational-quality, randomized, controlled clinical trial (RCT) of darbepoetin alfa Q3W administered at a fixed-dose of 300 mcg vs placebo in 300 patients were presented at the American Society of Hematology meeting in Atlanta, Georgia (Taylor, Ganly et al., 2005). The abstract and poster are provided for your reference (**Section 7.1.1**). The manuscript is currently in progress.

A study of darbepoetin alfa 300 mcg Q3W evaluated the effect of treating with darbepoetin alfa when administered at hemoglobin concentrations ≥ 10.5 g/dL and ≤ 12.0 g/dL vs when administered once hemoglobin concentrations are < 10 g/dL to achieve target hemoglobin levels (Rearden, Charu et al., 2004). The manuscript is currently in progress.

Another study demonstrated similar efficacy regardless of whether darbepoetin alfa (6.75 mcg/kg) was administered synchronously (ie, on the same day as) or asynchronously with Q3W chemotherapy (Glaspy, Henry et al., 2005). This study also evaluated pharmacokinetics, and reported a terminal half-life of approximately 74 hours, which is compatible with Q3W dosing. A copy of the manuscript is provided for your reference (**Section 7.1.1**).

A summary of published outcomes and doses for darbepoetin alfa administered Q3W is provided in **Table 4-1**.

Table 4-1. Dosing of Darbepoetin alfa Q3W – New Data from Published Studies

	Based on Minimally Effective Dose			Based on Recommended Starting Dose	
	Weight based	Fixed		Weight based	Fixed
Dose/number of Patients	4.5 mcg/kg n = 32	300 mcg n = 1493	300 mcg n = 196	6.75 mcg/kg n = 17	500 mcg n = 353
Average Weekly/Q3W Dose Administered	NR	105.4 mcg/ 323.6 mcg	NR	NR	125.2 mcg/ 375.6 mcg
Transfusion % (95% CI) (Week 5 to EOTP)	25 (9, 41)	18 (16, 20)	24 (NR)	NR	23 (19, 28)
Hematopoietic Response K-M% (95% CI)	51 (33, 70)	63 (61, 66)	NR	52 (27, 78)	NR
Hemoglobin 11 g/dL or greater Unadjusted K-M% (95% CI)	NR	79 (77, 81)	77 (70, 84)	NR	73 (68, 78)
Quality of Life	FACT-F increased with hemoglobin	4.7 point increase in FACT-F	NR	FACT-F increased with hemoglobin	57% with ≥ 3-point increase FACT-F
Reference	Kotasek *Eur J Cancer* (2003). (Dose-finding)	Boccia *Oncologist* (2006).	Taylor *Blood* (2005). (Placebo)	Kotasek *Eur J Cancer* (2003). (Dose-finding)	Canon *JNCI* (2006). (Registrational)

Note: NR = not reported

4.2.2 The FDA Approved Use of Darbepoetin alfa 500 mcg Q3W Leading to Updated US Prescribing Information for Darbepoetin alfa

To date, the FDA has approved 2 dosing regimens for darbepoetin alfa in the chemotherapy-induced anemia setting, QW dosing at 2.25 mcg/kg and Q3W dosing at 500 mcg, and has provided recommendations for dose adjustments (Amgen Inc., 2006). For both dosing schedules, the prescribing information directs physicians to adjust the dose for each patient to maintain a target hemoglobin concentration at a level not to exceed 12 g/dL. If the hemoglobin exceeds 13 g/dL, doses should be temporarily withheld until the hemoglobin falls to 12 g/dL. At this point, therapy should be reinitiated at a dose 40% below the previous dose (1.35 mcg/kg for QW and 300 mcg for Q3W). If the rate of hemoglobin increase is more than 1.0 g/dL per 2-week period or when the hemoglobin exceeds 11 g/dL, the dose should be reduced by 40% of the previous dose. For patients receiving weekly administration, if there is less than a 1.0-g/dL increase in hemoglobin after 6 weeks of therapy, the dose of darbepoetin alfa should be increased up to 4.5 mcg/kg.

Economic analysis based commonly administered doses including QW, Q3W and other compendia-supported doses leads to the conclusion that Medicare and its beneficiaries pay about the same or less for darbepoetin alfa than for epoetin alfa.

4.2.3 Comparable Clinical and Dose Outcomes with QW and Q3W Darbepoetin alfa

In summary, clinical trials evidence supports the efficacy of Q3W dosing, using either a 500 mcg or 300 mcg dose regimen. Appropriate use of dose escalation and reduction rules results in similar drug utilization to that seen using a 200 mcg Q2W approach (with dose escalation to 300 mcg Q3W) that has been submitted to CMS previously (eg, 114.5 mcg per week (Glaspy, Vadhan-Raj et al., 2006)) (**Table 4-2**).

Table 4-2. Outcomes and Average Weekly Doses in Published Studies

	Canon et al (2006)		Boccia et al (2006)	Glaspy et al (2006)	
	2.25 mcg/kg QW	500 mcg Q3W	300 mcg Q3W	200 mcg Q2W	40,000 U QW
Percentage of Patients Receiving Transfusions (Week 5 to EOTP)	30%	23%	18%	21%	16%
Average Weekly Dose	108 mcg	125 mcg	105 mcg	114.5 mcg[a]	42,714 U
Percentage of Patients Achieving Hemoglobin ≥ 11 g/dL	77%	84%	79%	80%	86%

[a] Average dose administered reported as 229 mcg Q2W (~ 114.5 mcg QW).

This new clinical evidence suggests that appropriate dose titration is more important for achieving high quality clinical outcomes and efficient utilization, than the dose used at initiation (which has been the main focus of debate regarding the clinical comparability of erythropoiesis-stimulating agents over recent years). Darbepoetin alfa allows physicians the flexibility to initiate at a lower dose ('minimally effective dose', 100 mcg per week and ratios thereof) and to dose escalate when necessary; or to initiate at a higher dose and dose reduce to maintain target hemoglobin levels. Both approaches appear to result in equivalent clinical outcomes and similar drug utilization.

4.3 EVIDENCE FOR QUALITY-OF-LIFE BENEFITS WHEN PATIENTS ARE TREATED WITH DARBEPOETIN ALFA CONTINUES TO GROW

Summary of Section

- Both meta-analyses and individual studies support treating anemia to improve patient HRQoL.
- Improvements in hemoglobin have been demonstrated to be associated with improvements in fatigue, anxiety, depression, energy, and activity levels.
- Improving fatigue, as measured by FACT-Fatigue, has also been shown to be associated with increasing patient productivity and activity as well as decreasing caregiver burden.
- Evidence-based guidelines recommend treating anemia to improve patient HRQoL.

The relationship between increased hemoglobin levels and improved health-related quality of life (HRQoL) in cancer patients with anemia has been demonstrated in a

number of prospective and retrospective studies (see below[5]). Increases in hemoglobin levels can result in improvements in the following aspects of patients' HRQoL: level of fatigue, levels of anxiety and depression, activity and energy levels, and overall HRQoL (for example, (Tchekmedyian, Kallich et al., 2003; Cella, Kallich et al., 2004; Littlewood, Kallich et al., 2006))(**Table 4-3**). Further, reducing fatigue has been demonstrated to improve patient productivity and overall activity and to decrease caregiver burden (Berndt, Kallich et al., 2005)(**Table 4-3**). These improvements have been observed regardless of tumor types, types of chemotherapy, and responsiveness to chemotherapy (see below[5]). Further, it appears that patient knowledge of hemoglobin value was not extensive and did not affect their responses on the FACT-F subscale (Kallich, McDermott et al., 2006).

[5] (Abels 1992; Case, Bukowski et al. 1993; Leitgeb, Pecherstorfer et al. 1994; Ludwig, Sundal et al. 1995; Glaspy, Bukowski et al. 1997; Kurz, Marth et al. 1997; Demetri, Kris et al. 1998; Glimelius, Linne et al. 1998; Malik, Khan et al. 1998; Dammacco, Castoldi et al. 2001; Gabrilove, Cleeland et al. 2001; Littlewood, Bajetta et al. 2001; Crawford, Cella et al. 2002; Glaspy, Degos et al. 2002; Kallich, Tchekmedyian et al. 2002; Vansteenkiste, Pirker et al. 2002; Hedenus, Adriansson et al. 2003; Shasha, George et al. 2003; Littlewood, Kallich et al. 2006)

Table 4-3. Summary of HRQoL Observations in Key Studies

Study	HRQoL Observations
Littlewood et al (2006) *Randomized, placebo-controlled trial of 344 patients with lymphoproliferative cancer and anemia due to chemotherapy treated with darbepoetin alfa* *(Mean age: 64.8 years)*	• Increasing hemoglobin is significantly associated with improvements in fatigue scores ($P < 0.001$). • Patients with clinically meaningful increases in FACT-Fatigue (FACT-F) scores had significantly greater ($P < 0.001$) increases in all other measures of HRQoL. • Significant improvements in anxiety and depression scores, as measured by the Brief Symptom Inventory, were observed in patients with improvements in FACT-F ($P < 0.001$). • Similarly, improvements in energy, activity, and overall health scores were observed when FACT-F improved ($P < 0.001$).
Tchekmedyian et al (2003) *Randomized, double-blind, placebo-controlled trial of 250 patients with lung cancer and anemia due to chemotherapy treated with darbepoetin alfa* *(Mean age: 61.4 years)*	• Many patients reported anxiety (25%) and depression (35%) at baseline, based on Brief Symptom Inventory. • Improvements in FACT-Fatigue score were correlated with improvements in Brief Symptom Inventory anxiety and depression scores ($P < 0.001$).
Cella et al (2004) *Based on 5 randomized trials in which over 1152 patients completed scales including FACT-Anemia (FACT-An) and energy, activity, and overall health* *(Mean age: 63.3 years)*	• In this analysis across 5 trials involving patients on or off chemotherapy, improvements in hemoglobin yielded meaningful improvements in fatigue and in physical, functional, emotional and overall well-being.
Berndt et al (2005) *Randomized, open-label, active-controlled, dose-finding trial in 300 patients with solid tumor cancers with anemia due to chemotherapy treated with darbepoetin alfa* *(Mean age: 60.8 years)*	• Patients were 61 years old on average. • One point improvements in FACT-Fatigue score corresponded to: o Increased productive time by 1 hour (95% CI, 0.5 to 1.5) o Reduced caregiver time burden by 0.7 hour (95% CI, 0.4 to 1.0) o Increased overall activity by 1.6% 95% CI, 1.4 to 1.7)

In their recent report (**Section 4.4.1**), AHRQ stated, "*Overall, QoL measures tended to favor treatment with epoetin or darbepoetin.*" This conclusion was supported by the Ross et al (2006) meta-analysis that observed significant improvements in HRQoL with erythropoiesis-stimulating agent treatment (see **Section 4.4.2.2**). In this meta-analysis,