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June 8, 2007

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RE: National Coverage Analysis for Erythropoiesis Stimulating Agents (ESAs) for
Non-Renal Disease Indications (CAG-00383N)

With more than 24,000 members worldwide, the American Society of Clinical Oncology (ASCO) is the leading medical society for physicians involved in cancer treatment and research. ASCO submits the following comments and clinical discussion (see addendum) in response to the recent proposed decision memorandum regarding coverage of erythropoiesis stimulating agents (ESAs) in non-renal disease indications (CAG-00383N). In our view, the proposal is premature and should be withdrawn pending future decisions by the Food and Drug Administration (FDA), which is the federal agency entrusted by Congress with the authority to make science-based recommendations on the usage of drugs and biologics.

The Centers for Medicare & Medicaid Services (CMS) is well aware that FDA convened a meeting of its Oncologic Drugs Advisory Committee (ODAC) on May 10 to review the full range of issues and data related to the use of ESAs in cancer patients, and that FDA is now considering the recommendations from ODAC, possibly with an eye toward additional amendments to the labeling for these products beyond the labeling's already mandated "black box" warnings. ASCO has no insight into what the final decision may be, but we have confidence that FDA will base its decision on the relevant science and data in the best interest of cancer patients.

We do not believe that the lawful decision of FDA concerning recommendations for usage should be preempted by CMS's coverage decision, which is not only inconsistent with the Medicare statute but also unsupported by the available medical evidence as outlined in the attached clinical discussion.

Legal Considerations

The Medicare statute was amended in 1993 to restrict the ability of CMS and its contractors to deny reimbursement for drugs and biologics used in cancer chemotherapy. Section 1861(t)(2) of the Social Security Act (42 U.S.C. §1395x(t)(2)) defines covered drugs as including "any drugs or biologics used in an anticancer chemotherapeutic regimen for a medically accepted indication." A "medically accepted indication" includes "any use which has been approved by the Food and Drug Administration," as well as uses supported

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by references in medical compendia that have not been specifically determined by the Secretary to be medically inappropriate.

Therefore, CMS lacks authority to make coverage decisions that are narrower than the FDA-approved indications. Moreover, additional uses unapproved by FDA but referenced in the statutorily identified medical compendia must be covered by Medicare absent a specific decision by the Secretary that such uses are medically appropriate.

The proposed decision memorandum is completely inconsistent with these Medicare provisions and must accordingly be withdrawn. CMS should await the decision by FDA, if any, to further revise or restrict the labeling for ESAs. No CMS coverage proposal should be issued that is inconsistent with the FDA-approved labeling or with the compendia listings unless they are found to be medically inappropriate.

Summary of Evidence-Based Concerns

Myelodysplastic Syndromes

ASCO does not believe there is evidence to support the non-coverage of ESAs in “anemia of myelodysplasia.” While it is not an approved indication, use of ESAs in the context of myelodysplastic syndromes (MDS) is well established in practice, supported by listing in a statutorily accepted compendium, and recommended in the joint guidelines of ASCO and the American Society of Hematology (ASH).

A number of published studies have confirmed the safety and efficacy of ESAs in MDS. Most significantly, a randomized, double-blinded, placebo-controlled trial compared ESAs with placebo in patients with low-risk MDS not receiving chemotherapy, with significantly more patients achieving a hematologic response in the ESA group; adverse events were the same in both the ESA and placebo groups. Many prospective and retrospective cohort studies and single-institution reviews have confirmed the findings in the randomized trial. Accordingly, there is a clear evidence basis for coverage of ESAs in MDS, and the Medicare law requires a positive coverage determination on account of the compendium listing.

Erythropoietin Receptors

CMS proposes imposition of coverage limits in connection with “ESA use by beneficiaries with tumors with erythropoietin receptors.” This proposal is not only unsupported by medical evidence; it is also completely impractical, as there is no reliable test to identify such receptors, nor is there is proven clinical significance to their existence. Responsible coverage policy should provide predictable and transparent results, which would be impossible with respect to the theoretical and unsubstantiated role of erythropoietin receptors. In short, there is no demonstrated clinical significance to the existence or not of erythropoietin receptors, and they should not serve as the trigger for non-coverage decisions that are inconsistent with the Medicare law as well as with evidence-based medicine.



Treatment Regimens Including Anti-Angiogenic or Anti-EGFR Drugs

With virtually no evidentiary support, CMS proposes to restrict use of ESAs with treatment regimens including drugs such as bevacizumab that have anti-angiogenic properties or drugs like panitumimab that are directed against the epidermal growth factor receptor (EGFR). There is no basis in law or in medical evidence to support such restrictions, and ASCO strongly opposes them. While it is true that these agents are unlikely to induce anemia when used individually, they will in many circumstances be administered in conjunction with chemotherapy drugs that do have anemia-inducing qualities. In any event, the proposed restrictions are inconsistent with the FDA-approved labeling and the compendia.

Initiation of ESA Therapy

CMS's proposed restrictions on initiation of ESA therapy appear to have no basis in clinical evidence. The proposed initiation levels are less than those indicated by relevant clinical trials. Indeed, in contrast to the CMS proposal, the overwhelming majority of clinical trials involving ESAs enroll patients with hemoglobin above 9 at baseline.

ESA Dosing

There is no evidentiary basis for the dosing restrictions proposed by CMS, leaving the perception that the restrictions are proposed for the sole purpose of limiting expenditures. CMS should cover ESAs consistent with the FDA-approved labeling, as required by law.

Duration of ESA Therapy

The CMS proposal would limit duration of ESA coverage to a total of 12 weeks per calendar year. This limit has no basis in evidence and could be extremely detrimental to patient care. Many chemotherapy regimens continue beyond 12 weeks, and patients may receive more than one such regimen per year, particularly in the recurrent, metastatic or palliative setting. An arbitrary limit of 12 weeks of coverage per calendar year could require patients either to forgo medically necessary additional chemotherapy or alternatively to endure transfusions as a result of treatment.

Limiting Coverage of ESAs to Clinical Studies

ASCO strongly opposes the suggestion that ESAs, as products approved for marketing by FDA, should be available to Medicare beneficiaries only in the context of clinical studies. That suggestion is inconsistent with the cancer coverage provisions imposed on CMS by Congress, is unmindful of the critical role of FDA in determining the safety and efficacy of marketed products, and is insensitive to the needs of cancer patients who benefit from these products. We reject the notion that products that have passed through the rigorous safety and efficacy screen of FDA review should be subjected to additional review through clinical studies required by Medicare officials as a precondition of reimbursement.



Conclusion

The proposed decision memorandum must be withdrawn and coverage restrictions for ESAs held in abeyance pending FDA revisions, if any, to the product labeling. Medicare law does not permit coverage limits that are more restrictive than the science- and evidence-based decisions of FDA regarding the usage of marketed drug or biologic products. CMS coverage decisions with respect to ESAs, as with other cancer therapies, must be based on FDA-approved labeling and supporting references in the statutorily recognized medical compendia.

Sincerely,

A handwritten signature in black ink that reads "Joseph S. Bailes". The signature is written in a cursive, flowing style.

Joseph S. Bailes, MD
Chair, Government Relations Council

**Addendum:
Clinical Discussion**

On May 14, CMS released a Proposed Decision Memorandum for Erythropoiesis Stimulating Agents for Non-Renal Disease Indications (CAG-00383N). Several of the restrictions included in that Memorandum are of deep concern to ASCO and should not be adopted by CMS. Below is a review of the available scientific evidence relevant to our objections regarding the proposed policy.

Myelodysplastic Syndromes

CMS proposes non-coverage of “the anemia of myelodysplasia,” however, there is no evidence in the PDM of the rationale behind this decision for myelodysplastic syndromes (MDS). While use in MDS is not an indication on the FDA label, it has been used off-label in this setting for many years, is a covered indication in one of the accepted compendia (the USPDI), and is recommended by the ASCO/ASH guidelines.¹ The USPDI lists epoetin as “accepted” in the setting of MDS, in “selected patients”; the ASCO/ASH guidelines recommend its use in low-risk MDS.

Multiple published studies have confirmed the safety and effectiveness of ESAs in the setting of MDS. A randomized, double-blind, placebo-controlled trial directly compared epoetin to placebo in patients with low-risk MDS not receiving chemotherapy.² Significantly more patients receiving epoetin achieved a hematologic response; adverse events occurred at the same frequency in the two groups.

Many prospective and retrospective cohort studies and single-institution series have confirmed the findings of the randomized trial. Published data have shown a QOL benefit,^{3,4} a reduction in transfusion requirements,⁴ and hematologic response/increase in hemoglobin levels.³⁻⁷

Erythropoiesis-stimulating agents (ESAs) have frequently been used in conjunction with granulocyte colony-stimulating factors (G-CSF) or granulocyte-macrophage colony-stimulating factors (GM-CSF); a recent randomized controlled trial showed that response to epoetin could be improved with the addition of G-CSF to the treatment regimen⁸; additional studies support this combined use in prolonged treatment.⁹

Moreover, a recent publication on the results of a Markov decision analysis performed on almost 800 low-risk MDS patients reported that, in the “good growth factor predictive” group, initial therapy with growth factors (ESAs, G-CSF, and/or GM-CSF) improved survival compared with non-growth factor treatments.¹⁰

Erythropoietin Receptors

CMS proposes that ESA treatment is “only reasonable and necessary under specified conditions for the treatment of anemia [in] those types of cancer in which the presence of erythropoietin receptors on either normal tissue/cell lines or malignant tissues/cell lines has been reported in the literature.” The PDM provides a list of these cancers, which “include but are not necessarily limited to,” breast, colorectal, lung, and prostate, among others. For these cancers, CMS proposes the following limitations (discussed in more depth throughout this response): baseline hemoglobin <9 at ESA initiation of dosing for the month; maximum covered treatment duration of 12 weeks per calendar year; maximum covered four-week treatment dose of 126,000 U for epo and 630 mcg for darbepoetin; non-coverage if there is evidence of poor drug response (hemoglobin rise <1 g/dL) after four weeks of treatment; and non-coverage if there is a rapid rise in hemoglobin >1 g/dL after two weeks of treatment.

In the Analysis section, CMS states that “(i)n particular, appropriate limitations should be applied to ESA use by beneficiaries with tumors with erythropoietin receptors.” It is assumed that CMS intends that to mean in patients with tumors that have been discussed in the literature as possibly possessing erythropoietin receptors, and not that each patient should have tumor samples individually tested for erythropoietin receptors. As discussed below, there is no commercially available, validated, reliable test that is sensitive and specific for erythropoietin receptors.

While CMS cites an extensive list of studies suggesting the presence of erythropoietin receptors on both normal and malignant tissue lines/cells, the agency does not fully convey the controversy and uncertainty in this field of research.¹¹⁻¹⁴ Importantly, and as highlighted by several authors and investigators, the currently available antibody tests directed against the erythropoietin receptor are not adequately specific for erythropoietin receptors.^{13,15-17} For example, Henke et al,¹⁸ in a retrospective analysis of head and neck cancer patients treated with radiotherapy and randomized to epoetin beta or placebo, employed the C20 polyclonal EpoR antibody, which has been shown to be nonspecific, binding to many targets.¹⁵ The largest area of overlap appears to be with heat shock proteins,^{15,16} which are abundantly expressed in a large array of cancers. The authors of the retrospective analysis of head and neck cancer patients acknowledge the “limited specificity” of this antibody in detecting erythropoietin receptors.¹⁹

Even if solid evidence were available on the presence of erythropoietin receptors on malignant cells, there is controversy regarding the functionality of these receptors on tumor cells.¹⁴ Amongst the many published preclinical studies examining this issue, there are conflicting findings on the effects of erythropoietin binding to the receptor, ranging from encouraging apoptosis of cancer cells, to a sensitization to chemo- or radiotherapy, to enhanced tumor proliferation.

Until there is a test for erythropoietin receptors that is both sensitive and specific, it is impossible to interpret the existing literature in terms of its relevance to clinical treatment with ESAs. Henke et al¹⁸ found a trend for locoregional progression in head and neck cancer patients who tested positive for erythropoietin receptors by immunohistochemistry but who were in the control (non-epoetin) arm of their study. However, with the exception of this one study cited by CMS, the existing data is preclinical, and it is not clear how well these data apply to the clinical setting. No studies using a sensitive and specific antibody for erythropoietin receptors have been designed to prospectively investigate the role of erythropoietin receptors in tumor progression in the clinical setting.

Treatment Regimens Including Anti-Angiogenic Drugs (Such as Bevacizumab) or Monoclonal/Polyclonal Antibodies Directed Against EGFR

CMS proposes non-coverage of ESAs for patients receiving anti-angiogenic agents such as bevacizumab or monoclonal/polyclonal antibodies directed against EGFR. There is no clinical evidence of benefit when an ESA is given in conjunction with monotherapy with either drug class, and there is no clinical evidence of harm if an ESA is given to treat mild to moderate chemotherapy-induced anemia when either of these drug classes are used concurrently with chemotherapy. The proposed restriction on ESAs in “treatment regimens including” these two classes (anti-angiogenic drugs and antibodies directed against EGFR) has no evidence to support it.

Define Baseline Hemoglobin for Initiation of ESAs

CMS provides little rationale for proposing this change. CMS acknowledges that the level at which anemia requires intervention is not well established, and that “by tradition” patients have received transfusions at hemoglobin levels of 7 or 8. CMS goes on to cite the British Blood Transfusion Society,²⁰ whose guidelines state that transfusions are indicated in patients with hemoglobin levels less than 7, and should not be used in patients with hemoglobin greater than 10. Further citing the BBTS, CMS states that the management of patients with hemoglobin levels between 7 and 10 “remains unclear.”

Nowhere in the PDM is there a clear link between the evidentiary base and CMS’ determination that hemoglobin must decrease to 9 before initiating ESAs. Indeed, the overwhelming majority of ESA trials enrolled patient groups with mean or median hemoglobin above 9 at baseline. When reported, the standard deviations and ranges show that nearly half the included patients had hemoglobin concentrations well above 10, even in most randomized controlled trials with means or medians below 10.²¹⁻²³ Therefore, it is not clear which, if any, studies informed CMS’ decision on this point.

ESA Dose

There is no specific discussion of the evidence CMS used to arrive at the maximum 4-week dose it proposes.

According to the FDA-approved label²⁴ (and the ASCO/ASH guidelines), a standard 4-week course of epoetin with weekly epoetin would use 160,000 U epoetin SC (4 x 40,000 U). CMS is proposing a maximum of 126,000 U over this timeframe. For darbepoetin, CMS proposes a maximum of 630 mcg over 4 weeks; the FDA-approved label²⁵ approves 2.25 mcg/kg for weekly dosing. It appears that CMS is using a standard of a 70 kg person in making these calculations (2.25 mcg x 70 kg x 4 = 630 mcg darbepoetin; 150 U x 70 kg x 12 = 126,000 U epoetin). If this is the case, any patient weighing over 70 kg will likely be under-dosed under the proposed regulations. Furthermore, the proposed restrictions would not allow for weekly dosing of epoetin (at the approved dose of 40,000 U SC) in accordance with the FDA-approved label.

In addition to the limitations described above, this 4-week dose limitation does not allow for dose escalation (see below). Finally, this proposed restriction puts yet another burden on patients with MDS. Patients with MDS may require higher doses of ESAs to achieve a response, but as noted above, that response may be durable, may spare patients blood transfusions, and may even contribute to increased survival. Limiting ESA dose in patients with MDS who are responding to higher doses has no support in published evidence.

Hypo-Responders / Dose Escalation

There is no specific discussion of how CMS arrived at this provision. The proposed policy—to stop ESA treatment if the hemoglobin increases less than 1g/dL after 4 weeks of therapy—does not put forward a strong evidence base for such a restriction. CMS states that a high ESA dose requirement may contribute to or portend increased risk for thrombotic-vascular events, and that many cancer patients manifest erythropoietin resistance, but they fail to tie these concepts back to the results of clinical trials or to the proposed restriction.

Much of the published literature on dose escalation is based on study designs that utilized built-in upward titration of ESAs in “non-responders.” A significant proportion of these initial non-responders achieved a hematologic response with higher doses, and the FDA-approved label clearly allows for and details the specific doses used in dose escalation. It is also important to keep in mind that in clinical use, ESAs are dosed to achieve specific hemoglobin targets or ranges, a situation which does not lend itself to setting an artificial limit on overall ESA dose.

Other Dose Adjustment

No evidence is explicitly linked to the proposal to stop ESA treatment if the hemoglobin increases by more than 1g/dL after two weeks. As noted above, CMS discusses concern surrounding the rate of hemoglobin rise in a general way, and it seems that this proposed restriction arises from CMS’s concern, discussed throughout the PDM, that supraphysiologic doses of ESAs could promote tumor progression, through the ESA’s purported effects on erythropoietin receptors on tumors.

The current FDA-approved labels^{24,25} give clear direction for dose adjustment in those patients who manifest a vigorous response to ESAs, and as also noted above, ESAs are titrated to achieve and maintain hemoglobin targets/ranges. In combination with the proposed CMS restriction which would not allow ESA initiation until the hemoglobin drops to 9, and taking into account that it may take several weeks for a hemoglobin response to be observed, this restriction could cause a patient on myelosuppressive therapy to be below a hemoglobin of 10 throughout therapy, even with ESA treatment (and beyond, depending how long marrow recovery would be expected to take).

Duration of ESA Therapy

CMS proposes limiting duration of coverage to a total coverage of 12 weeks per calendar year. There is no strong link between the evidence and the proposed regulation. Many randomized controlled



trials examining ESAs were 12 weeks in duration -- some were 16-20 -- but CMS presents no correlation between length of study/therapy and adverse events.

As importantly, many chemotherapy regimens may last beyond 12 weeks, a common example being dose-dense chemotherapy for adjuvant treatment of breast cancer.^{26,27} Patients with a variety of malignancies may receive regimens extending beyond 12 weeks, or more than one chemotherapy regimen per year, particularly in the recurrent or metastatic/palliative setting. An arbitrary cutoff of 12 weeks of coverage per calendar year could place patients and providers in the position of having to consider forgoing a second (or beyond) chemotherapy treatment regimen in one calendar year or, alternatively, force these patients into the transfusion setting.

Patients who can potentially stand to gain from the use of ESAs could be adversely affected by this proposed restriction. It essentially limits ESA use to one chemotherapy regimen per year for those patients with CIA and, even assuming CMS lifts the overall restriction on use in patients with MDS, these patients would still be adversely affected by the 12-week rule, as studies have shown durable and sustained responses over much longer periods of time in these patients, even up to one and two years.

Coverage of ESAs Only Within Clinical Trials

CMS states that, “we are also interested in public comment on whether coverage for ESA therapy for Medicare beneficiaries with cancer should occur only within appropriately designed clinical research studies where informed consent and safety monitoring can be assured.”

This restriction: ignores the results of dozens of randomized, controlled trials; preempts the FDA’s authority in the drug approval process; and is an unprecedented move to restrict coverage for a drug based on results from studies selectively cited by CMS and/or extrapolations made from in vitro studies or from studies in non-indicated settings to proven clinical indications.

General Comments/Conclusion

ASCO believes that CMS has gone far beyond the currently available evidence—as well as beyond actions taken by the FDA-- in many of the proposed restrictions to ESA use.

We feel that in many of the restrictions proposed by CMS the preponderance of the evidence supports continued coverage of ESAs by CMS. ESAs should continue to be covered for anemia induced by chemotherapy or chemoradiotherapy and for the anemia of MDS, without the arbitrary dosing restrictions proposed by CMS. ESAs should be prescribed judiciously, with patient safety and benefit, as always, being the determining factors in any decision to utilize these agents.

References:

1. Rizzo JD, Lichtin AE, Woolf SH, et al: Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol* 20:4083-107, 2002
2. A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes. *Br J Haematol* 103:1070-4, 1998
3. Stasi R, Abruzzese E, Lanzetta G, et al: Darbepoetin alfa for the treatment of anemic patients with low- and intermediate-1-risk myelodysplastic syndromes. *Ann Oncol* 16:1921-7, 2005
4. Spiriti MA, Latagliata R, Niscola P, et al: Impact of a new dosing regimen of epoetin alfa on quality of life and anemia in patients with low-risk myelodysplastic syndrome. *Ann Hematol* 84:167-76, 2005
5. Giraldo P, Nomdedeu B, Loscertales J, et al: Darbepoetin alpha for the treatment of anemia in patients with myelodysplastic syndromes. *Cancer* 107:2807-16, 2006
6. Mannone L, Gardin C, Quarre MC, et al: High-dose darbepoetin alpha in the treatment of anaemia of lower risk myelodysplastic syndrome results of a phase II study. *Br J Haematol* 133:513-9, 2006
7. Musto P, Lanza F, Balleari E, et al: Darbepoetin alpha for the treatment of anaemia in low-intermediate risk myelodysplastic syndromes. *Br J Haematol* 128:204-9, 2005
8. Balleari E, Rossi E, Clavio M, et al: Erythropoietin plus granulocyte colony-stimulating factor is better than erythropoietin alone to treat anemia in low-risk myelodysplastic syndromes: results from a randomized single-centre study. *Ann Hematol* 85:174-80, 2006
9. Mantovani L, Lentini G, Hentschel B, et al: Treatment of anaemia in myelodysplastic syndromes with prolonged administration of recombinant human granulocyte colony-stimulating factor and erythropoietin. *Br J Haematol* 109:367-75, 2000
10. Sekeres MA, Fu AZ, Maciejewski JP, et al: A Decision analysis to determine the appropriate treatment for low-risk myelodysplastic syndromes. *Cancer* 109:1125-32, 2007
11. Agarwal N, Gordeuk VR, Prchal JT: Are erythropoietin receptors expressed in tumors? Facts and fiction--more careful studies are needed. *J Clin Oncol* 25:1813-4; author reply 1815, 2007
12. Jelkmann W, Laugsch M: Problems in identifying functional erythropoietin receptors in cancer tissue. *J Clin Oncol* 25:1627-8; author reply 1628, 2007
13. Osterborg A, Aapro M, Cornes P, et al: Preclinical studies of erythropoietin receptor expression in tumour cells: impact on clinical use of erythropoietic proteins to correct cancer-related anaemia. *Eur J Cancer* 43:510-9, 2007
14. Hardee ME, Arcasoy MO, Blackwell KL, et al: Erythropoietin biology in cancer. *Clin Cancer Res* 12:332-9, 2006
15. Elliott S, Busse L, Bass MB, et al: Anti-Epo receptor antibodies do not predict Epo receptor expression. *Blood* 107:1892-5, 2006
16. Brown WM, Maxwell P, Graham AN, et al: Erythropoietin receptor expression in non-small cell lung carcinoma: a question of antibody specificity. *Stem Cells* 25:718-22, 2007
17. Della Ragione F, Cucciolla V, Borriello A, et al: Erythropoietin receptors on cancer cells: a still open question. *J Clin Oncol* 25:1812-3; author reply 1815, 2007
18. Henke M, Mattern D, Pepe M, et al: Do erythropoietin receptors on cancer cells explain unexpected clinical findings? *J Clin Oncol* 24:4708-13, 2006

19. Henke M, Mattern D, Pajonk F: Correspondence, In Reply to Della Ragione et al and Agarwal et al, JCO 2007 25:1813-1814. J Clin Oncol 25:1815, 2007
20. Murphy MF, Wallington TB, Kelsey P, et al: Guidelines for the clinical use of red cell transfusions. Br J Haematol 113:24-31, 2001
21. Seidenfeld J, Piper M, Bohlius J, et al.: Comparative effectiveness of epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment. Comparative Effectiveness Review No. 3. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-02-0026. Rockville, MD: Agency for Healthcare Research and Quality., May 2006
22. Seidenfeld J, Aronson N, Piper MA, et al.: Use of erythropoietin for anemia in oncology: Evidence Report/Technology Assessment No 30 (AHRQ Publ No. 01-E009). Prepared by the Blue Cross and Blue Shield Association Evidence-based Practice Center under Contract No. 290-97-0015. Rockville, MD, Agency for Healthcare Research and Quality, June 2001
23. Bohlius J, Wilson J, Seidenfeld J, et al: Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev 3:CD003407, 2006
24. Epogen/Procrit Product Label. Revised 03/09/07 Available at: <http://www.fda.gov/cder/foi/label/2007/103234s5122lbl.pdf> Accessed 6/7/07
25. Aranesp Product Label. Issue date: 04/2007 Available at: http://www.amgen.com/pdfs/misc/aranesp_pi.pdf Accessed 06/07/07
26. Citron ML, Berry DA, Cirrincione C, et al: Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 21:1431-9, 2003
27. Burstein HJ, Parker LM, Keshaviah A, et al: Efficacy of pegfilgrastim and darbepoetin alfa as hematopoietic support for dose-dense every-2-week adjuvant breast cancer chemotherapy. J Clin Oncol 23:8340-7, 2005