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Fighting Bone Marrow Diseases through Patient Support & Research Since 1983

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June 13, 2007

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RE: Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs)
for non-renal disease indications (CAG-00383N)

Dear Dr. Phurrough:

On behalf of patients with rare bone marrow failure diseases, the Aplastic Anemia & MDS International Foundation (AA&MDSIF) is submitting comments to CMS on its Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N). The AA&MDSIF, a non-profit organization with a volunteer Medical Advisory Board comprised of prominent experts in the field, is extremely concerned that CMS has proposed eliminating coverage of ESAs for the anemia of myelodysplasia or of myelodysplastic syndromes (MDS).

We should first state that the AA&MDSIF has no financial incentives to support or to oppose the CMS recommendations in the proposed decision memo; our only incentives are the interests of patients. We also recognize that ESAs are not appropriate for all patients and not all patients with bone marrow failure respond to ESAs. Still, many patients with bone marrow failure benefit from ESAs. If there were evidence that these growth factors were generally inappropriate for MDS patients, the Foundation would actively and promptly inform our patients of the change in the scientific consensus. However, CMS has not provided the rationale necessary to refute this consensus.

As we noted in our comments dated April 13, 2007 on the CMS National Coverage Analysis (NCA) on the administration of erythropoiesis-stimulating agents for non-renal disease applications, ESAs promote red blood cell growth and are used to treat anemia in MDS patients. The most common signs and symptoms associated with MDS are related to anemia, and this practice is considered "accepted" (as opposed to "acceptance not established" or "unaccepted") in the USP-DI. Four published articles, two of which are surprisingly not listed in the CMS bibliography, support the use of ESAs in

MDS^{1 2}. Because of this listing in the USP-DI, Medicare covers this off-label use for MDS.

In addition to the research cited in the USP-DI, several other published studies support the use of ESAs for MDS patients. In fact, we submitted in our initial comments four such articles and meeting presentations. The MDS Foundation, another non-profit organization, submitted the three of the four same citations as well as three others for a total of six. We were dismayed to see none of those seven citations included in the bibliography to the proposed decision memo, yet according to the CMS website, “CMS considers all public comments, and is particularly interested in clinical studies and other scientific information relevant to the technology under (consideration).” We can only surmise that our comments were disregarded and not properly deliberated and hope that CMS will take a careful look at them at this point in the process. The paragraph with the four citations is repeated below.

In fact, there have been some studies of ESAs in bone marrow failure patients that do not demonstrate a negative impact. Studies assessing the long term use of Epo (with or without granulocyte colony-stimulating factors) in MDS patients compared to either randomized controls³ or historical controls^{4 5} have shown no negative impact on survival or on evolution to acute myelogenous leukemia (AML) with such treatment. In addition, the 2006 Jadersten et al study indicates improved survival in low-risk MDS patients with low transfusion need who have been treated with these agents. An even more recent article⁶ provides more evidence for improved survival in low-risk MDS patients. We are unaware of any data that would contraindicate the use of ESAs in responsive BMF individuals. The risk-benefit analysis of ESAs in MDS patients strongly favors their beneficial effect of minimizing blood transfusions in this highly compromised population, as a greater number of blood transfusions and resultant higher iron overload burden correlates with diminished survival in MDS patients.

In addition, we are surprised and disappointed that CMS issued the memo a mere two business days after the hearing of the Oncologic Drugs Advisory Committee (ODAC), part of the Food and Drug Administration (FDA). We believe that CMS should have waited for the panel of hematology and cancer experts (who had hundreds of pages of data plus a day of testimony to review) to weigh in on the matter. Incidentally, the ODAC meeting is not even mentioned in Section V “FDA

¹ Depaoli L, Levis A, Isabella N, Ficara F, Priotto C, Lista P, Foà R, Resegotti L. Serum erythropoietin level and marrow erythroid infiltration predict response to recombinant human erythropoietin in myelodysplastic syndromes. *Haematologica*. 1993;Mar-Apr;78(2):118-22.

² Stasi R, Brunetti M, Bussa S, Conforti M, Di Giulio C, Crescenzi A, Terzoli E, Vecchione A, Pagano A. Response to recombinant human erythropoietin in patients with myelodysplastic syndromes. *Clin Cancer Res*. 1997;May;3(5):733-9.

³ Miller KB, Kim HT, Greenberg P, van der Jagt R, Bennett JM, Tallman MS, Paietta E, Dewald G, Houston JG, Thomas M, Rowe J. Leukemia Committee, Eastern Cooperative Oncology Group, Brookline MA,; Leukemia Committee, Canadian Leukemia Study Group, Ottawa ON. Phase III Prospective Randomized Trial of EPO with or without G-CSF Versus Supportive Therapy Alone in the Treatment of Myelodysplastic Syndromes (MDS): Results of the ECOG- CLSG Trial (E1996), *Proc Am Soc Hematology meeting, Blood* 104 (11): 24a, 2004.

⁴ Jadersten M, Montgomery SM, Dybedal I, Porwit-MacDonald A, Hellstrom-Lindberg E. Long-term outcome of treatment of anemia in MDS with erythropoietin and G-CSF. *Blood* 106(3): 803-11, 2005.

⁵ Jadersten M, Malcovati L, Dybedal I, Della Porta MG, Invernizzi R, Montgomery SM, Pascutto C, Porwit-MacDonald A, Cazzola M, Hellstrom-Lindberg E. Treatment with Epo and GCSF improves survival in MDS patients with low transfusion need. *Proc Am Soc Hematology meeting, Blood* 108 (11): 158a, 2006.

⁶ Golshayan A, Jin T, Maciejewski J, Fu AZ, Bershady B, Kattan MW, Kalaycio ME, Sekeres MA. Efficacy of growth factors compared to other therapies for low-risk myelodysplastic syndromes, *Br J of Haematology* 137: 125-132, 2007.

Status,” although other FDA action is listed, including the black box warning which is clearly irrelevant to MDS.

As explained in our April comments, the studies that led to the FDA’s black box warning do not appear to have included any patients with bone marrow failure (such as MDS) but only patients who had end-stage solid cancers and/or renal disease. Moreover, in those studies, the patients’ hemoglobin levels typically were kept above 12 g/dl while bone marrow failure patients rarely reach a hemoglobin level that high even with the addition of growth factors. Thus findings from these studies cannot be said to apply to patients with MDS. In general, MDS patients do not share the same risks as patients who were part of the ESA studies on adverse events and have not experienced the same adverse events. Physicians of course still must monitor hemoglobin levels in bone marrow failure patients receiving ESAs, especially those with renal and/or heart disease, to ascertain that their levels do not rise above 12 g/dl.

We find that, in the proposed decision memo, CMS has made no scientific case for eliminating coverage of ESAs for MDS. In fact, CMS does not include in its proposed decision memo much background about the use of ESAs in MDS. A search of the memo for “myelodysplastic,” “myelodysplasia,” and “MDS” reveals that these terms are only rarely used. The term “myelodysplasia” is used only in listing “the anemia of myelodysplasia” as a condition to be no longer covered. The terms “myelodysplastic” and “MDS” are used only in one sentence in the entire text of the decision memo: “There has even been a report of the conversion of myelodysplastic syndrome (MDS) to leukemia attributed to erythropoietin’s angiogenic effects on the bone marrow (Bunworasate 2001, Ribatti 2002).” (from Section VIII “CMS Analysis”) Hence there are only two citations noted in the body of the text of the proposed decision memo that relate to MDS, and neither is a study: Bunworasate 2001 is just a case report and Ribatti 2002 is a letter to the editor in response to the case report.

Even if the case report of an MDS patient who progressed to acute monoblastic leukemia (AML) had definitely been caused by an ESA and not a natural progression of the MDS, the AML was *reversed* and not a cause of death. Moreover, it is only *one* case report published in 2001 and one letter published in 2002, with no similar publications since. (It is well known among clinicians that the blood counts of all patients on ESAs should be monitored to prevent adverse events.) If this progression were seen more often clinically, there would certainly be more case reports and possibly even studies on the development. Instead, there is a significant body of evidence to *support* using ESAs for MDS. In one 2007 article alone, the authors found 87 articles of more than 1500 MDS patients treated with ESAs for whom treatment and outcome were known.⁶ All of the guidelines cited in Section VII.B.5. “Evidence Based Guidelines/Professional Society Position Published Statements” support the use of ESAs for MDS or are silent on the matter; none opposes the use.

We are further concerned about the citations that CMS did include in its bibliography: they do not justify removing coverage of ESAs for MDS and in fact support the use of ESAs for MDS. For example, one randomized double-blind placebo-controlled study listed in the bibliography actually showed a significantly higher erythroid response in the ESA arm for refractory anemia patients and for non-transfused patients: “In conclusion, rHuEpo was effective in the treatment of low-risk MDS. RA subtype, no transfusions prior to rHuEpo therapy, and low basal Epo levels were

⁶ Golshayan A, Jin T, Maciejewski J, Fu AZ, Bershady B, Kattan MW, Kalaycio ME, Sekeres MA. Efficacy of growth factors compared to other therapies for low-risk myelodysplastic syndromes, Br J of Haematology 137: 125-132, 2007.

associated with higher probability of response. Soluble transferrin receptor level at the fourth week was an early predictor of response.”⁷ Another study on an ESA included in the bibliography found that “(r)esponses to therapy were durable and generally occurred at r-HuEpo doses of 150-200 U/kg t.i.w. There were no reports of thrombosis, seizures or therapy-related hypertension. The data show that patients with MDS, especially those with the RA and RARS subtypes, can benefit from treatment with r-HuEpo.”⁸ We cannot find in any of the studies listed in the bibliography a conclusion that warrants not covering ESAs for MDS.

With the exception of one sentence, in the proposed decision memo, the text to justify not covering ESAs for MDS does not even pertain to MDS. The diagnosis of MDS does not involve tumors, or vascular disease that can increase one’s risk for blood clots and strokes. MDS, cancer, and kidney disease are very different diseases, as the FDA and its ODAC recognize. In fact, Richard Pazdur, MD, Director of the FDA’s Office of Oncology Drug Products, firmly noted so in the May 10 hearing and promised a committee member that the FDA would work with CMS so that MDS patients did not lose coverage for ESAs because of the black box warning for kidney and cancer patients.

We agree with Dr. Pazdur. ESAs are a crucial part of treatment options for bone marrow failure patients. There are no alternatives to ESAs other than blood transfusions, yet blood transfusions are not a solution for this patient population. In addition to the issue of blood-supply shortages, MDS patients need irradiated platelets. Irradiated platelets can be difficult to obtain, and this need both complicates the process and increases the expense. Further, bone marrow failure patients who get transfusions typically have a chronic need for them (something not seen in cancer and chemotherapy patients). This chronic need for transfusions puts MDS patients at great risk for iron overload which is difficult alone for these patients but is especially problematic with the newly revised FDA warning on Exjade <http://www.fda.gov/medwatch/safety/2007/safety07.htm#Exjade>, a medication used to treat iron overload. This warning is relevant to MDS patients, so treating physicians will have to be particularly careful in devising a treatment regimen for MDS patients.

The significant expense of treating iron overload should also be calculated in the cost of a transfusion v. the cost of an ESA if CMS is considering cost factors in making its coverage recommendations. (CMS states in Section VIII “CMS Analysis” that “with limited exceptions, the expenses incurred for items or services must be ‘reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member’ (§ 1862(a)(1)(A)).”) CMS should also bear in mind that treatment options for MDS are limited and that most non-growth-factor medications for MDS work only 20-30% of the time and carry significant side effects.⁶⁹ Moreover, patients who take non-growth-factor medications may need ESAs in conjunction with those drugs.

⁷ Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes. A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. *Br J Haematol* 103:1070-4, 1998.

⁸ Rose EH, Abels RI, Nelson RA, McCullough DM, Lessin L. The use of r-HuEpo in the treatment of anaemia related to myelodysplasia (MDS). *Br J Haematol.* 1995 Apr;89(4):831-7.

⁶ Golshayan A, Jin T, Maciejewski J, Fu AZ, Bershady B, Kattan MW, Kalaycio ME, Sekeres MA. Efficacy of growth factors compared to other therapies for low-risk myelodysplastic syndromes. *Br J of Haematology* 137: 125-132, 2007.

⁹ Sekeres MA, Fu AZ, Maciejewski JP, Golshayan A, Kalaycio ME, Kattan MW. A decision analysis to determine the appropriate treatment for low-risk myelodysplastic syndromes. *Cancer.* 109(6):1125-1132.

Finally, the AA&MDSIF is concerned about the limitations for patients undergoing treatment for certain named cancers in the proposed decision memo. While MDS is not listed as one of the cancers affected (not surprisingly as MDS does not meet a definition of cancer used by the National Institutes of Health), we would object to two of those limitations being applied to MDS patients: 1.) “the maximum covered treatment duration is 12 weeks/year” and 2.), “continued use of the drug is not reasonable and necessary if there is evidence of poor drug response (hemoglobin/hematocrit rise <1 g/dl/<3%) after 4 weeks of treatment.” The first limitation is unfair to MDS patients who may need weekly transfusions. The second limitation should be modified to allow for eight weeks of treatment before determining that the patient is not responding.

CMS states in Section I of the proposed decision memo that it is specifically seeking comments on whether or not “there is sufficient evidence to conclude that erythropoiesis stimulating agent (ESA) treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease increases their risk of adverse effects related to ESA use. These conditions include...the anemia of myelodysplasia....” CMS clearly has not presented sufficient evidence to show that ESAs are not reasonable and necessary for patients with MDS: one case report on a reversed adverse event and a letter to the editor on the case report do not demonstrate that ESAs have “a deleterious effect...on their underlying disease” or that MDS “increases their risk of adverse effects related to ESA use.” Until there is sufficient evidence to show that ESAs harm MDS patients, the AA&MDSIF believes that Medicare coverage policy on ESAs for MDS should remain the same so as to not alter access to this effective treatment for MDS patients.

Thank you very much for taking the time to review our comments. If we can provide any additional information or answer any questions, please do not hesitate to contact us. We would be pleased to help CMS formulate an appropriate, science-based coverage policy.

Sincerely,

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