



APLASTIC ANEMIA & MDS INTERNATIONAL FOUNDATION, INC.
Fighting Bone Marrow Diseases through Patient Support & Research Since 1983

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RE: NCA Tracking Sheet for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)

Dear Ms. Ciccanti:

On behalf of patients with rare bone marrow failure diseases, the Aplastic Anemia & MDS International Foundation (AA&MDSIF) is submitting its comments to CMS for its National Coverage Analysis (NCA) on the administration of erythropoiesis-stimulating agents (ESAs) for non-renal disease applications. The AA&MDSIF, a non-profit organization with a volunteer Medical Advisory Board comprised of prominent experts in the field, is particularly interested in the use of ESAs for myelodysplastic syndromes (MDS). Because ESAs promote red blood cell growth, many of our constituents have benefited from these growth factors, which are prescribed off-label for patients with bone marrow failure diseases like MDS, aplastic anemia, and paroxysmal nocturnal hemoglobinuria (PNH). Medicare covers this off-label use for MDS because the practice is supported by research cited in the USP-DI. This finding is not surprising, considering that ESAs are approved to address anemia in certain patient populations and the most common signs and symptoms associated with MDS are related to anemia.

The Foundation appreciates the steps that CMS (as well as the Food and Drug Administration) is taking to ensure the safety of all patients who take medication. Given the studies that have shown significant and life-threatening events in certain patients who have taken these growth factors for non-renal diseases, this action by CMS is appropriate. However, these studies 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.

Further, the adverse events discovered in these studies—an increased risk of thrombotic events and stimulation of tumor growth—are not likely to be relevant to patients with bone marrow failure: this diagnosis does not involve tumors or vascular disease that can increase one's risk for blood clots and strokes. Both

of these potential problems are likely to involve non-erythropoietic effects of the growth factor erythropoietin (Epo) on endothelial cells or on tumors, where there are Epo receptors, although expressed at a low level. Moreover, most patients with bone marrow failure have low platelet counts, a condition which tends to decrease the chance of clotting.

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 controls¹ or historical controls^{2 3} 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 article⁴ 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, clinical practice guidelines published by American Society of Clinical Oncology and the National Comprehensive Cancer Network also support certain uses of ESAs for treatment of myelodysplasia in select patients. Further, the consensus from experts in hematology, based on their vast clinical experience, is that the MDS patients do not generally 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.

More studies on ESAs in bone marrow failure patients would help to better understand the drug and its impact on this unique patient group, but in the meantime, while the warning from the FDA must be assessed for each individual patient with bone marrow failure, CMS should continue to cover the administration of ESAs for MDS.

Thank you very much for your consideration of these comments. If the Foundation or any members of our Medical Advisory Board can provide you with any additional information, please let us know.

Sincerely,

Richard Stone, MD
Chairman, AA&MDSIF Medical Advisory Board
Dana Farber Cancer Center, Harvard University

¹ 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 (No. 11): 24a, 2004.

² 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 (No. 3): 803-11, 2005.

³ 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 (No. 11): 158a, 2006.

⁴ 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.

