

August 18, 2011

Janet Woodcock, MD
Director
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Avenue
Hillandale Building, 4th Floor
Silver Spring, MD 20993

Dear Dr. Woodcock,

On behalf of the American Society of Nephrology (ASN), a not-for-profit organization of more than 13,000 physicians and scientists dedicated to promoting excellence in the care of patients with kidney disease, please accept these comments regarding the recent changes in label, package insert, and dosing guidelines for Erythropoiesis-Stimulating Agents (ESAs).

ASN thanks the Food and Drug Administration (FDA) for its recognition of the importance of individualization as a key component of high-quality care in the recently updated recommendations regarding ESA therapy. The importance of individualized care in treating patients with kidney disease cannot be overstated. Every patient has different medical needs that require a unique plan of care, and preserving the integrity of the patient-physician relationship remains a top priority for the society.

Nonetheless, ASN is concerned that the recent ruling regarding ESA dosing may not be warranted based on currently available evidence, and could have adverse unintended consequences for the care of patients with kidney disease. Specifically:

- Currently available scientific evidence does not support elimination of a 10-12g/dL target hemoglobin range.
- The new label misrepresents results TREAT trial and does not account for the evidence gaps in ESA dosing strategies and target hemoglobin levels. There was no increase in the risk of myocardial infarction (heart attack) and the trial did not target hemoglobin levels of 11 g/dL. In fact, there was no difference in the composite cardiovascular outcome (and no difference in myocardial infarction) between the darbepoetin- and placebo-treated groups and the trial targeted hemoglobin levels of 13 g/dL.
- New dosing recommendation terminology could result in overly conservative, more rigidly enacted ESA dosing practice patterns in some dialysis units, potentially placing patients at increased risk of anemia and blood transfusions, which could adversely affect health and candidacy for transplantation.
- Further research examining ESA doses at various hemoglobin levels is needed to better elucidate the optimal course of ESA therapy.

New Label Does Not Accurately Reflect Current Evidence

The gaps in the current knowledge base regarding optimal ESA administration dose and timing remain considerable. As ASN testified at the Cardiovascular and Renal Drugs Advisory Committee meeting in October 2010, the society believes that the inferences that can be made from TREAT about the optimal label range are limited, and any justification for a label change based on TREAT is inherently weak. For a

variety of reasons, TREAT enrolled a healthier population than anticipated, with the majority of patients not necessarily requiring any ESA treatment even based on the 10-12 g/dL target range. A comparison of achieved mean hemoglobin concentrations among the four large ESA trials (TREAT, CREATE, CHOIR, and—in CKD patients undergoing dialysis—the Normal Hematocrit Study) puts the low hemoglobin groups in each of them well within the range of the previous 10-12g/dL recommendation. Every controlled trial of ESAs has studied a target hemoglobin level. Accordingly, it remains unclear whether complications or variations in responsiveness relate to ESA dosing strategy or target hemoglobin level.

Furthermore, the new label states that “patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dL.” This statement obscures the fact that patients enrolled in TREAT were actually assigned to darbepoetin alfa to achieve a hemoglobin of **13g/dL** (not 11g/dL, as the new label insinuates). Were TREAT to be repeated with patients assigned to achieve a hemoglobin of, for instance, 10g/dL or 11g/dL, different outcomes may have been observed. FDA should revise the new label to correct the inaccurate implication that patients experienced greater risks when targeted to *any* hemoglobin level above 11g/dL and state clearly that these risks were observed when targeted to 13g/dL.

Revised Terminology May Hamper Access to Appropriate ESA Therapy

ASN is concerned that the new label terminology may result in serious consequences for the vulnerable dialysis patient population, including increased use of transfusions to control for anemia—which have a detrimental effect on transplant outcomes. The new recommendations could prompt physicians (or patients) to be overly cautious and not administer (or decline to receive) ESAs in instances where the benefits may in fact outweigh the risks. In particular, the society is troubled that the label now instructs physicians that “if the hemoglobin level exceeds 11 g/dL, reduce or interrupt the dose of ESA.” Recommending that physicians “interrupt” ESA therapy could be interpreted to suggest that a physician should *necessarily* suspend ESAs if a patient’s hemoglobin level is 11.1g/dL.

From a pharmacokinetic perspective, proposing “interruption” of the ESA dose is not appropriate. ESAs stimulate the bone marrow to produce red blood cells. Interrupting the dose of ESAs in patients with ESRD causes the bone marrow to produce red blood cells in spurts—alternated with periods of no production—rather than at a more physiologically normal constant rate. The effects of interruptions in ESA dosing do not appear for several weeks, or even months. Re-initiation of ESAs at that time may be too late to avoid negative sequelae, such as transfusions. It is standard practice to modify the dose of ESAs, but not to interrupt it altogether. Accordingly, ASN recommends that FDA remove the word “interrupt” from the new ESA label.

While ASN appreciates FDA’s emphasis on individualizing care, the emphasis may be overshadowed by FDA’s pointed recommendation to wait to “initiate ESA treatment when the hemoglobin level is less than 10 g/dL,” and to “reduce or interrupt” ESA therapy at 11g/dL, for patients on dialysis, resulting in rigidified practice patterns in some dialysis units. Since every dialysis patient responds differently to ESA therapy, such rigidity could be to the detriment of some patients’ functionality and quality of life.

Concerns about increased rigidity are heightened by the advent of the new bundled payment system and pay-for-performance quality measures within the Medicare ESRD program, which recently established financial incentives for dialysis providers to administer fewer ESAs. ASN also notes that the new label could set a precedent for private payers to deny coverage of ESAs if patients’ hemoglobin levels exceed 10 or 11g/dL, further limiting individualized care for a diverse, vulnerable patient population.

New Label May Generate Inaccurate Perceptions of Risks and Benefits

ASN is also concerned that the new label focuses on the dangers of ESA therapy, but does not adequately convey the potential benefits of the medication for patients. Administered within the reasonable guidelines, and under careful supervision of a nephrologist, ESAs have for decades helped maintain patient functionality and quality of life. Most importantly, ESAs enable nephrologists to treat

kidney patients' anemia without resorting to blood transfusions, which can cause immune sensitization and reduce patients' likelihood of receiving and maintaining a transplant.

Maintaining patient comfort with, and access to, appropriate levels of ESAs is particularly important for patients who are women or who are members of certain minority groups. These populations often require higher doses of ESAs to achieve the same outcomes as other patients. Women and minorities are at a greater risk for requiring transfusions if their access to reasonable levels of ESA therapy is curtailed. As currently written new recommendations have the potential to create new and aggravate existing disparities in the access to kidney transplantation. FDA should revise the label to present a more balanced depiction of the potential risks and benefits of ESAs.

More Data are Needed to Understand the Most Appropriate Use of ESAs

As previously mentioned, every controlled ESA trial to date has examined target hemoglobin levels. It remains unclear whether complications or variations in responsiveness relate to ESA dosing strategy or target hemoglobin level. Future studies examining ESA doses at various hemoglobin levels would help to further elucidate the optimal course of ESA therapy. ASN encourages FDA to call for and support this important area of research.

On behalf of ASN, thank you for your willingness to consider our comments on the recent changes to ESA labeling and package insert policies. We appreciate FDA's commitment to ensuring the most safe and efficacious use of the therapies that affect the lives of our patients and stand ready to work with FDA on this and any other nephrology-related issue. To discuss ASN's comments, please contact ASN Executive Director Tod Ibrahim at tibrahim@asn-online.org or (202) 640-4676.

Sincerely,



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