

**Transcript of FDA's Media Briefing on
Dosing Recommendations for Erythropoiesis Stimulating Agents**

**Moderator: Kimberly Rawlings
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Coordinator: Welcome and thank you for standing by. At this time all participants are in a listen-only mode. After the presentation we will conduct a question and answer session. To ask a question you may press star 1. Today's conference is being recorded. If you have any objections, you may disconnect at this time. I would now like to turn the meeting over to your host for today's conference, Ms. Kimberly Rawlings. You may begin.

Kimberly Rawlings: Thank you, (Teresa). Welcome ladies and gentlemen. Again, my name is Kimberly Rawlings and I'm with the FDA Center for Drug Evaluation and Research in the Office of Communications. This is an FDA teleconference for credential media to get information on the FDA release about the dosing recommendations for ESAs.

We have spokespersons today - we have two speakers today from CDER that will provide opening remarks, Dr. Richard Pazdur from - he's the Director of the Office of Oncology Drug Products and Dr. Robert Kane, the Acting Director - Acting Deputy Director, excuse me, for Safety in the Division of Hematology Products. Actually there's one correction, Dr. Kane will be

providing opening remarks and Dr. Pazdur will be here to provide any technical assistance. We also have with us Dr. Anne Farrell who is the Acting Director of the Division of Hematology Products in the Office of Oncology, excuse me, Oncology Drug Products who will be available to provide technical expertise as well.

After the speakers make brief remarks we will move to the question and answer segment. Reporters will be in listen-in-only mode until we open up the call for questions. When asking a question please state your name and affiliation. Also please limit yourself to one question and one follow-up so we can get as many questions in as possible.

The news release for this announcement has been sent to reporters on our media list as well as posted to the FDA Web site at www.fda.gov. At this time I'll turn the call over to Dr. Kane. Thank you.

Dr. Robert Kane: Thank you, Kim. Today FDA is recommending new, more conservative dosing recommendations for the ESAs, which is an abbreviation for Erythropoiesis-Stimulating Agents, when they're used to treat a specific type of anemia which occurs in patients with chronic kidney disease. These recommendations are being added to the boxed warning and other sections of the drug's package inserts or physician labeling because of the risk of cardiovascular events in this patient population.

More than 20 million people aged 20 years or older in the United States have chronic kidney disease and as this disease worsens, patients typically have to initiate dialysis or may be eligible for kidney transplantation.

With progressive kidney disease, patients lose their ability to produce red blood cells which are the main oxygen-carrying cells of the body. We call this

progressive condition anemia and anemia is commonly measured by a number expressing the amount of a protein, hemoglobin, which is in the blood.

Drugs in the ESA class include Epogen, Procrit and Aranesp all manufactured by Amgen. These ESAs are synthetic versions of a human protein known as erythropoietin and this protein stimulates the bone marrow to produce red blood cells. The ESAs are used to treat certain types of anemia and they help patients reduce their need for blood transfusion which is the only principal alternative management for this form of anemia.

Previously the drug labels for Epogen, Procrit and Aranesp recommended that these drugs be dosed to achieve and maintain hemoglobin levels within the range of 10 to 12 grams in patients with chronic kidney disease. The new package labeling removes this previous concept that there was a generally applicable target hemoglobin range.

Clinical trials have shown that there's an increased risk of cardiovascular events such as heart attack and stroke and death when patients receive ESA treatment to target a hemoglobin level of greater than 11. And also the evidence indicates that patients do not obtain any additional benefit to these higher targets when compared to lower hemoglobin targets.

As a result, the new ESA labels will now recommend first of all that physicians and their patients with chronic kidney disease should weigh the possible benefits of using these drugs to decrease the need for red blood cell transfusions against the increased risk for serious adverse cardiovascular events. For each patient individualize dosing and use the lowest dose of Aranesp sufficient to reduce the need for red blood cell transfusions.

For patients with chronic kidney disease who are not on dialysis, the label indicates to consider starting ESA treatment only when the hemoglobin level is less than 10 grams and when certain other considerations apply. If the hemoglobin level exceeds 10 grams per deciliter, reduce or interrupt the dose of ESA.

For patients with chronic kidney disease who are on dialysis, the risks and benefits are different than those not on dialysis. The label states that ESA treatment may be appropriate when the hemoglobin level is less than 10. The statement says to initiate when the hemoglobin is less than 10. In other words, do not initiate when the hemoglobin level is greater than 10. How far below 10 to initiate is a clinical judgment considering the potential risks and needs for each individual. No target range is stated because it is not possible to specify a target hemoglobin that can be identified as effective or safe for one individual.

The label also states reduce or interrupt the use of ESA if the hemoglobin level approaches or exceeds 11 grams. The reason for the difference numerically between the two groups is the fact that the risks and benefits, responsiveness to the drug and individual needs are different between the two population groups.

This statement does not say to target or to achieve a hemoglobin of 10 or a hemoglobin of 11. The statement reinforces the evidence that serious risks have been demonstrated when the hemoglobin target is above 11. What is best for an individual patient has to be judged for that individual patient and the intention of the new labeling is to encourage the flexibility for individual dosing.

The new label provides guidelines about when to initiate ESA therapy, when to modify dosing and when to stop or interrupt therapy, taking into consideration the needs of each individual patient. Rather than dosing for a specific hemoglobin target, physicians are asked to individualize dosing to each patient's unique circumstance and to use the lowest possible ESA dose that can reduce the need for blood transfusions.

Individual patients vary in their response to ESAs. Hemoglobin levels fluctuate normally in each individual. Also the rate of change of hemoglobin values over time has to be anticipated. The intention was to provide for flexibility and individual care in this label.

Thank you.

Kimberly Rawlings: Thank you Dr. Kane. At this time we will begin the question and answer portion of the briefing. Operator, we'll take our first question.

Coordinator: Thank you. If you'd like to ask a question, please press star 1. You will be announced prior to asking your question. To withdraw your question, please press star 2. Once again, to ask a question, please press star 1. One moment please.

Once again, to ask a question, please press star 1.

Kimberly Rawlings: We also ask that when you ask your question if you could please identify yourself and give your affiliation as well.

Coordinator: Kathryn Foxhall of Drug Topics Magazine, you may ask your question.

Kathryn Foxhall: Yes. This is Kathryn Foxhall of Drug Topics - covering for Drug Topics Magazine. How does a physician know what the suitable dose is to prevent the need for transfusion? Is it if you're not targeting a particular level in the blood?

Dr. Robert Kane: I think I understand your question to be the dosing of the drug is based on the observation over time for each individual patient. And there is likely to be a plausible range of hemoglobin values that work best for that individual. This is something that will have to be derived over a period of time and investigation.

I want to point out that we're not stating that these drugs are able to prevent transfusions in patients with chronic kidney disease. The evidence to date indicates that there is some degree of reduction of the amount of transfusion but unfortunately they do not appear to be able to prevent it at doses that are acceptable to use today.

So the answer to your question is that each physician knowing their individual patient's needs, pro-morbidities, other factors, rate of consumption of the blood in which it has to be replaced, has to individualize that decision and observe it over time. There is a need for flexibility in dosing and this is a practice of medicine type of issue that goes beyond what we can specify in a written label document.

Kimberly Rawlings: Thank you. We'll take our next question.

Coordinator: Gardiner Harris of New York Times, you may ask your question.

Gardiner Harris: Hi. Thanks so much for taking my question. I guess I have a few questions. I mean, why now? This has obviously been sort of an ongoing process for years

about ESA dosing, why are you taking this action now? Is there some particular data out there that has particularly alarmed you to the toxicity of ESAs in this setting? And why the difference in - have those data suggested that there is a real sort of difference in the population?

And then finally what about the ongoing clinical trial? I think there's a clinical trial by Amgen called the TREAT trial I believe in which they've got to target an adequate level of I think 13. I mean I haven't followed this closely for some time. But are those - is that clinical trial appropriate, should it continue? Thanks.

Dr. Robert Kane: I think your question touches on several points and if I don't cover them all we may come back to it.

Gardiner Harris: Okay.

Dr. Robert Kane: The TREAT clinical trial is completed and published.

Gardiner Harris: Okay, sorry.

Dr. Robert Kane: You're correct that the target in the dosing arm for Darbepoetin Aranesp was 13. There was considerable assessment as this trial proceeded and concern on many sides whether it should complete to its conclusion. Numerous times during the trial people looked for safety signals that might indicate that it should not run to conclusion and never during the conduct of the trial did that threshold cross where it appeared that it would not be safe to continue to completion.

And in fact the overall outcome of that trial has been interpreted by some as a neutral outcome that is neither indicating a clear overall effect one way or the

other. But within that trial there is an important safety finding after the trial is completed and could be analyzed that there was a clear increase in stroke in patients receiving the Aranesp treatment to the target hemoglobin of 13. That increase was even more evident if you looked at individuals in the Darbepoetin treatment group with an underlying prior history of stroke.

All of these things in total indicate a pro-thrombotic effect of ESAs. It is not clear at this point that there is a hemoglobin level below which you might not have any of these problems. It's also clear that as the hemoglobin target increases the risk increases.

So the TREAT trial is in the history books already. The analysis of the TREAT trial has been an extensive process by FDA including a presentation of the findings at a public advisory committee last October. Since that time, additional queries and analysis and questions have been carefully deliberated and worked through leading to the ability now to state in the new label what we have concluded to be the appropriate path forward for treatment today.

Gardiner Harris: Okay. And are there - I'm sorry to abuse you and keep asking questions but is there any - I know Dr. Pazdur is on the line here and these drugs are used in the cancer setting as well, you are not addressing the cancer setting in this advisory today but is there any worry additionally in the cancer setting that we should know about?

Dr. Robert Kane: You're correct that the specific changes of dose and administration being made right now apply to the patient population with chronic kidney disease. It is true that these drugs have an application of use in patients with the anemia that is a result of chemotherapy treatment for cancer patients. These dose and administration changes do not directly affect that population. However, in the other parts of this new label, specifically the warnings, precautions and boxed

warning statements, these statements which reiterate and extend our concern about the risk apply to all patients.

Dr. Richard Pazdur: Gardiner, the reason why I'm here is that the application was reviewed by the Division of Hematology Drug Products which falls under the Oncology Office. In relationship to your other question about something that initiated this, this was a process that has been in review of these trials have been going on for many, many months and the subject of several advisory committee and we wanted to get various stakeholder's input on the issues because they are very difficult to really address many of these.

Gardiner Harris: Thank you so much.

Kimberly Rawlings: Thank you. We'll take our next question, Operator.

Coordinator: Sandra Young of CNN, you may ask your question.

Sandra Young: Yes. Thank you for taking my question. I'm trying to get a little bit more information on the increased risks of the cardiovascular events. Do we have numbers, specifically the number of strokes, heart attacks and even deaths that have been directly linked to the dosing of ESAs?

Dr. Robert Kane: We have numbers. You'll see in the new label, within Section 5, a new table which summarizes each of the three major randomized control trials that have provided the information about risk. So I'll refer you to those tables and not go into more detail specifics right now. I think that's your best source of information.

Sandra Young: Thank you.

Kimberly Rawlings: Thank you. And those labels are posted to our Web site.

Saundra Young: Thank you.

Kimberly Rawlings: We'll take our next question. Lynne Peterson of Trends-in-Medicine, you may ask your question.

Lynne Peterson: Thank you. Do these new rules have any implications for other erythropoietin agents in development?

Dr. Robert Kane: I think that the short answer to that would be that for drugs in development it's not possible to make any statement at this point. Those kinds of decisions and processes would be issues that would have to be determined as the drug progresses through development up to the time of approval. So I think we are not able to give you any specific reply to that question at this time.

Lynne Peterson: And I have a follow-up.

Kimberly Rawlings: (Unintelligible) follow-up.

Lynne Peterson: Thank you. Will it change any of the trial designs or will it affect any other ongoing trials of another agent where they have to modify their protocols?

Dr. Robert Kane: I think that that's a very good observation that each trial and each review board will have to take into consideration at this point.

Kimberly Rawlings: Thank you. Thank you. We'll take our next question.

Coordinator: Rebecca Voelker of JAMA, you may ask your question.

Rebecca Voelker: Yes. Hi. You mentioned the 20 million people 20 and over have chronic kidney disease but can you estimate how many people are taking these drugs or how many patients may be affected by these new label recommendations?

Dr. Robert Kane: With regard to patients affected I think that this would be of importance to all patients with chronic kidney disease. The - with regard to specific numbers, no I do not have that information at hand. Other sources - since patients who go on dialysis become eligible for Medicare, that could be one source of the information that might help you.

Rebecca Volker: Thank you.

Coordinator: Once again, if you'd like to ask a question, please press star 1. Jon Wolleben of BioCentury Publications, you may ask your question.

Jon Wolleben: Hi. I was wondering if you could provide a little more details about the additional trials that Amgen will be required to conduct, specifically any timeframes that you may have right now.

Dr. Robert Kane: This is obviously of great importance both to the company and to us. We are embarking upon trials that will attempt to identify better, safer dose regimens, strategies for the use of these drugs under defined circumstances. We think that we still need more fundamental clinical information before another major trial can go. So this is a work in progress and a lot of attention is being given to it.

Kimberly Rawlings: Great. Thank you very much, Dr. Kane. Ladies and gentlemen, this concludes today's media teleconference. Thank you for your participation. A replay will be available in about an hour and will be up for about three days for your listening. If you have any follow-up questions, please don't hesitate

to call the FDA's Office of Public Affairs. That number is 301-796-4540, again, 301-796-4540. Thank you.

Coordinator: This concludes today's conference call. Thank you for your participation.

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