Trends-in-Medicine

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Quick Pulse

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The cardiac safety of erythropoiesis-stimulating agents (ESAs) was not a major topic or concern at the major nephrology meeting in Europe, ERA-EDTA. Eleven European nephrologists were interviewed, and many do not believe that ESAs are cardiotoxic, at least not the way they use them in Europe, which is more conservatively than some American doctors. If there is a problem, it's an American problem, European nephrologists said. They said their use of ESAs has not changed, and they do not expect European guidelines or labels to be revised.

BACKGROUND

Data from two trials, published in the ***New England Journal of Medicine*** and announced at the American Society of Nephrology meeting in November 2006, ignited a firestorm of controversy over the appropriate use and safety of ESAs. In the U.S., there have been congressional hearings, an FDA Advisory Committee (with a second Advisory Committee planned for September 2007), new KDOQI guidelines proposed, restrictions on Medicare coverage, and payor restrictions on reimbursement.

The CHOIR and CREATE trials suggested – but did not definitely prove – that there is increased mortality with ESAs when hemoglobin is targeted >12 g/dL in chronic kidney disease (CKD) patients.

- **CHOIR** – a randomized clinical trial in anemic chronic renal failure patients which found that hemoglobin >13 g/dL increased the risk of heart attack, death, and stroke. This trial studied 1,432 patients with chronic kidney disease (pre-dialysis) treated with Johnson & Johnson's Procrit/Eprex (epoetin alfa) to boost levels of hemoglobin in the blood. Half the patients were treated with a hemoglobin goal of 13.5 g/dL and the other half with a target of 11.3 g/dL. This open-label study, sponsored by J&J, was stopped early in May 2005 by the data safety monitoring board (DSMB) because of an excess of cardiovascular adverse events. Researchers found that patients with the higher hemoglobin target had a 33.7% increased risk of death, MI, or stroke, and their "strong recommendation was to target hemoglobin of 11-12 g/dL in all CKD patients."
- **CREATE** – an international trial of 603 patients with Stage 3-4 CKD and mild-to-moderate anemia (hemoglobin 11-12 g/dL) who were given Roche's NeoRecormon (epoetin beta). In one arm, the hemoglobin target was 13-15 g/dL, and in the other arm the target was 11-12.5 g/dL. Investigators found that the higher hemoglobin target did not reduce cardiovascular events (the primary endpoint) or all-cause mortality, and the risk of congestive heart

failure (CHF) also was higher, but the time to dialysis was significantly shorter. At Year 1, quality of life was better in the high-target group, and this benefit was maintained out to Year 2. An investigator said, "CREATE supports the current guidelines. It does not endorse routine hemoglobin normalization."

Also in November 2006, the FDA issued a public advisory on the use of ESAs in CKD patients, warning that "patients treated with an ESA and dosed to a target hemoglobin of 13.5 g/dL are at a significantly increased risk for serious and life threatening cardiovascular complications, as compared to use of the ESA to target a hemoglobin of 11.3 g/dL." The FDA urged doctors to follow the existing prescribing information for all ESAs currently approved in the U.S. – Amgen's Aranesp (darbepoetin alfa), Amgen's Epogen (epoetin alfa), and Johnson & Johnson's Procrit/Eprex (epoetin alfa), all of which are manufactured by Amgen. The FDA also recommended that the target hemoglobin not exceed 12 g/dL.

In March 2007, the FDA put a black box warning on all ESAs approved in the U.S. The FDA also revised the product labels for these drugs, with updated warnings and modifications to the dosing instructions, and it warned physicians to use as little of them as possible. FDA officials said this action was based on studies that found an increased risk of death, blood clots, strokes, and heart attacks in patients with chronic kidney failure when ESAs were given at higher than recommended doses and on studies which found more rapid tumor growth in patients with head and neck cancer who received these higher doses.

Based on its review of CHOIR and five other trials, the FDA had four messages for patients and physicians:

1. Use the lowest dose of ESA that will gradually increase hemoglobin concentrations to the lowest level sufficient to avoid blood transfusions.
2. ESAs increase the risk for death and serious cardiovascular events when administered to target hemoglobin >12 g/dL.
3. A higher incidence of deep vein thrombosis (DVT) has been documented in patients receiving epoetin alfa prior to blood transfusions who did not receive prior anticoagulation therapy.
4. For cancer patients, an ESA:
   a. Shortened overall survival and increased death attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy, when administered to a target hemoglobin >12 g/dL.
   b. When administered to head and neck cancer patients getting radiation, shortened the time to progression when hemoglobin was targeted >12 g/dL.
   c. Increased mortality in cancer patients not receiving chemotherapy or radiotherapy when targeting hemoglobin >12 g/dL. An FDA official declared, "ESAs are ***not*** indicated for these patients."

The Center for Medicare and Medicaid (CMS) also announced in May that it was opening a National Coverage Analysis (NCA) on the use of ESAs for conditions other than end-stage renal disease (ESRD) – i.e., use in cancer patients. This was the first step toward issuing a National Coverage Determination (NCD). Currently, CMS pays for ESAs needed to maintain a target hemoglobin level of 10-12 g/dL and reduces payment if hemoglobin exceeds 13 g/dL unless the dose is reduced.

In May 2007, the FDA's Oncologic Drugs Advisory Committee (ODAC) decided the black box warning was not enough. Citing concerns about the safety of ESAs, the panel voted 15-2 that the FDA should impose additional restrictions on ESA use. The panel also voted unanimously that additional safety trials are needed. Panel members expressed dismay at the dearth of valid data from ***any*** trials and expressed concern at the evidence that showed ESAs decrease survival and, in fact, may promote tumor growth. The FDA's Cardio-Renal advisory committee will meet in September on ESA use in patients with chronic renal failure.

European View of the Cardiac Safety of ESAs

European nephrologists are watching the U.S. reaction to this issue. Most sources were ***dubious that ESAs are cardiotoxic***, suggesting that, if there is a problem, it relates more to how the drugs are used in the U.S. than an inherent problem with ESAs. Comments included:

- *U.K.:* "People are still skeptical about the reality of this toxicity, and the CREATE trial is still on-going, so the cardiovascular disease risk is not clear. There has been lots of criticism of the CHOIR trial, but in CREATE they did not show any harm with high hemoglobin although it did show improvement in quality of life. So, my feeling is still in favor of higher hemoglobin which should still be beneficial."
- *Italy #1:* "ESAs have been a problem in the U.S. According to a recent trial (CREATE), certain hemoglobin targets should not be exceeded. Rather, patients should be on target. The problem was that American doctors went to very high levels of hemoglobin. Data from DOPPS (Dialysis Outcomes and Practice Patterns Study) show that the average hemoglobin in Europe is about 11 g/dL, so that means that most patients are still under-treated, and only a minority are over the upper limit and into the level of undesirable targets. Although definitive data should be produced, the perception here is that over-treatment of anemia is not a problem in most European countries."

- *Dr. Francesco Locatelli of Italy, past-president of ERA-EDTA:* "I do not have any concerns about the cardiac safety of these drugs. The problem is there is no discussion about the partial correction of anemia. Partial correction of anemia is absolutely fantastic for improving patient survival and quality of life. So, the real discussion is about normalization of anemia. The present guidelines suggest partial correction of anemia, maintaining a hemoglobin level of between 11 and 12 g/dL. If you look at the two trials published in the ***New England Journal of Medicine*** a few months ago – CHOIR and CREATE (I was the author of one and the referee of the other one, so I know the trials very well) – the control group had a hemoglobin target exactly in the values suggested by the guidelines. So, we can say that this trial was saying that there was no advantage – and there may be some disadvantage – in normalizing the hemoglobin level while, according to the control group, which was the guideline group, it means you have to stay within the guidelines."
- *Germany:* "I'm not concerned about their cardiac toxicity …I don't think there really is cardiac toxicity with these agents."
- *Ireland:* "I'm not so much concerned about the cardiac safety as what my (hemoglobin) targets should be…(The increased CV events) may be related to the EPO, but it's difficult to blame them entirely…We have to be very careful about drawing too many conclusions about some of the studies because the baseline doses of EPO that were used in these studies – particularly in the CHOIR study – really were very high, higher than we would normally use in Europe. So, perhaps the dosage was important, at least in that study."
- *Macedonia:* "We read about the toxicity in the published studies (CHOIR and CREATE), and we discussed this in our department (at a university). Right now, there is a project sponsored by Roche, with about 60 patients with CKD who are not on dialysis and are being treated with EPO in order to maintain higher hemoglobin levels – but not high enough to have a high risk of CV events. We did not terminate this study when we read about the cardiac toxicity."

Yet, some European nephrologists have been convinced there ***is a safety issue*** with ESAs:

- *Dr. Iain Macdougall, U.K.:* "I am concerned about cardiac toxicity. I think these days, it's not just the absolute hemoglobin levels that matters, it's also the process of getting there. The big studies that were published at the end of last year – CREATE and CHOIR – suggested that 11-12 g/dL is probably about right for hemoglobin and anything above 13 is an absolute no-no. We should not go above 13 g/dL and use caution between 12 and 13. I'm on the U.S. KDOQI guidelines board (the Anemia Work Group), and (new targets) will be published in September. The draft is in the public domain already, and the final draft will be very similar. I believe in everything that is in that draft."
- *Czech Republic:* "Of course, we are concerned because we know that cardiac problems are a major concern for hemodialysis patients in terms of their quality of life and survival. In some cases, I think that these agents may precipitate these cardiac events."
- *U.K. #2:* "The trials have basically said this is a problem."
- *Switzerland:* "We have personally had a few problems with patients whose hemoglobin levels went too high. We started too fast, and levels went up too high, and we had real problems with shunt dysfunction and fistula dysfunction, both due to high hemoglobin. We also had two or three patients who developed peripheral vein thrombosis and some hypertension, too. So, we have had some problems when we gave too high a dose, and hemoglobin goes up too high."

A poster by Czech researchers reported on a retrospective study which concluded that EPO treatment for renal anemia may increase the risk of thrombosis of arteriovenous fistulae. The researchers looked at 475 dialysis patients from 1995 to 2003 and found a correlation between higher hemoglobin and the number of thromboses per 1,000 dialysis sessions, though the correlation was not statistically significant.

IF THERE IS A CARDIAC PROBLEM WITH ESAS – WHY?

If ESAs do have a cardiac risk, what is the mechanism? Is it how high the hematocrit is pushed, how much total dose the patient gets, or a specific problem with ESAs? European nephrologists generally believe the issue is the total dose a patient gets. Comments included:

- *Czech Republic:* "I think an elevated hematocrit is only part of the whole effect that can influence the risk of cardiac events. I'm not sure about the nature of the agents themselves, but I think that the **total dose** also affects this risk."
- *Macedonia:* "I don't know which it is. You obviously achieve higher hemoglobin values with higher doses of these agents. I think the main problem in treated patients is that these agents lead to **higher viscosity of the blood** because they increase the number of erythrocytes, and maybe this is the main reason for the cerebrovascular disorders that are mentioned in CHOIR and CREATE. It could be the **dose** or the **patients themselves**, but I'm not sure it's just the agents."
- *Italy:* "The problem of dose exists, and I think the **dose** is very important in causing these (cardiac) effects. You need to tailor the dose to the hemoglobin level, and if the dose is excessive, toxicity is more likely."

- *Switzerland:* "We…focus more on hemoglobin levels and not the direct toxicity of ESAs. There probably are toxic side effects from EPO therapy, so a **direct damaging effect**. It might also be related to the dose, but we haven't really looked at that."
- *Germany:* "I think it's an **anemia-related phenomenon**, related to the correction of anemia, and I think it's not wise to over-correct anemia. But as long as you keep within the range of the guidelines, I think these agents are okay."
- *U.K. #1:* "I think it's **the process by which you get up to your hematocrit**. It's more than just the hematocrit. I don't think the hematocrit itself is a problem, rather it's a composite of hematocrit vs. the **amount of ESA** to get there."
- *U.K. #2:* "There might be an association between **dose** and toxicity – that's my feeling – rather than toxicity being caused by the rheostatic effects of a higher hematocrit. So, I think it's total dose."

HEMATOCRIT TARGETS

The move to a higher hemoglobin target (13 g/dL) hadn't really become common in Europe, sources said. As a result, European nephrologists said they aren't having to lower their hemoglobin targets. Rather, the proposed new KDOQI Clinical Practice Guidelines on Anemia and CKD target of 11-12 g/dL is what they were using – and are continuing to use. Comments included:

- *U.K. #1:* "In the U.K., they have just introduced a new set of standards in the last 12 months in which they re-evaluated the old standards, and the new targets are 10.5-12.5 g/dL. These limits were set because of data from the clinical trials."
- *Italy #1:* "(CREATE) confirmed that the guidelines were right. I was a liaison member of the KDOQI guidelines committee, and maybe during the last year, the KDOQI guidelines changed in terms of moving the target from 11-12 to 11-13. Now, there is an updating to go back again to a range of 11-12, but, importantly, not to intentionally aim for >13. In the trials, you intentionally increase the hemoglobin levels in patients randomized to a particular group. It doesn't matter how much EPO you have to use. In clinical practice, you give the patients a small amount of drug. Some patients respond very well. Some have difficulty responding. But once you reach 11 or 11.5 g/dL, we stay there because there is no reason to go higher…If the hemoglobin level is too high, you have the risk of thrombosis, and it affects blood pressure as well. So, you need to be very careful and not correct anemia too fast, or this could be a problem…At the doses suggested by the guidelines, there is no risk, and there are data suggesting that this correction could be good."
- *U.K. #2:* "Our current practice is based on NICE (National Institute of Clinical Excellence) guidelines, so the target is 12.5. It doesn't say to higher than that."
- *Ireland:* "My targets now, particularly in view of recent studies such as CREATE and CHOIR, are aimed towards a hemoglobin of 11-12 g/dL rather than any higher than that…My own personal preference – and more or less the European preference – would have been not to go much higher than that anyway. So, it (the safety issue) has not really altered my own individual preference or strategy."
- *Czech Republic:* "When these agents became available for use, we started with very low levels of baseline hematocrit, and in the early years we were limited in our use of these drugs by budgets, so (hemoglobin) levels were not as high as the recommended levels. But we generally use the lower limits of the recommendations now during the whole time (of treatment). In my opinion, the target should be ~11.5 g/dL. So, we are maintaining patients between 10.5 and 12.0, and we were doing this the whole time as we were a bit skeptical about higher hemoglobin levels like 13.0."
- *Macedonia:* "In our department, we always stick to a target hemoglobin of 11-12 g/dL. All the time, that is our target. It has not changed because of these trials."
- *Italy #2:* "Our approach has not changed at all. We believe that over-correction of anemia is not a good approach…We believe that in patients with cardiovascular conditions and problems with vascular access, it is better to maintain hemoglobin levels at target between 11 and 12 g/dL…We start the use of EPO at a hemoglobin <11 g/dL, and we continue this therapy until we can maintain hemoglobin at target between 11 and 12 g/dL."
- *Switzerland:* "We look more to the hemoglobin levels. We don't use hematocrit much in Europe, but we don't go over 120, if it goes over 120, we lower it. But in Europe we really use hemoglobin, and here we aim for 110 to 120 (11-12 g/dL). Within these targets, I feel that the ESA drugs are safe to use…There is probably a move now towards not having hemoglobin levels too high."
- *Germany:* "The European targets have changed only a little bit, quite similar to the U.S. target, so we're targeting patients to between 11 and 12 g/dL. But the upper limit is not precisely defined. At our center, we did not change our policy regarding the application of EPO targets…I think it is good and essential to keep an eye on the upper limits of hemoglobin levels, just in order not to over-correct anemia…Definitely not go over 13. And I think you should start a down-correction of the hemoglobin when the patient is above 12."
- *U.K. #3:* "My hematocrit targets changed. I used to be happy going up to 13 g/dL, but now I'm trying to get to between 11 and 12 g/dL. Of course, you can't stay exactly between 11 and 12 – that's too tight – but you try."

European Payor and Government Perspective

European payors, mostly government health programs, have not changed reimbursement rules for ESAs, and sources do not expect any changes.

- *Italy:* "There has been no change from a European regulatory point of view."
- *Ireland:* "My government has not reacted to this yet. We're a much smaller country, and we tend to follow the lead from Europe and the U.K.…But I think labeling changes, as in advice regarding dosage, would be appropriate."
- *Czech Republic:* "These agents are paid for by the insurance companies in the Czech Republic…Right now, there are no exclusion criteria to the use of these drugs."
- *Macedonia:* "We are under pressure all the time to monitor our drug use, not just the EPO drugs but all the expensive drugs, and this has not changed since the big studies came out…I don't anticipate seeing a change in the labeling of these products."
- *U.K.:* "We follow the NICE guidelines…but I don't think they have yet corrected these guidelines based on the new clinical trial evidence…My personal feeling is labeling changes are ***not*** necessary."
- *Germany:* "No, none. The drugs are approved for patients with renal anemia in all stages, and we can use them in all patients with renal anemia, and this has not changed."

Overall Use of ESAs

European use of ESAs has historically been more conservative than U.S. use. Thus, sources do not believe ESA use overall in Europe will decline as a result of cardiac safety issues. A Czech nephrologist said, "I wouldn't say the use of these agents has declined because of safety concerns. We had one case of pure red cell aplasia (PRCA) using these drugs, but this did not influence our administration of the medication. This patient now doesn't receive this medication, but he maintains sufficient hemoglobin levels." A U.K. doctor said, "I wouldn't say that use has declined, but I think people are more aware of keeping hemoglobin within a target range rather than pushing levels up as high as they can." Another U.K. doctor said, "We've had no changes in EPO use at all. Nothing has changed because the hematocrit we're aiming for is 12.5 g/dL, and at that level we think it's safe." An Irish doctor added, "I think this (safety issue) may affect how much EPO may be prescribed, particularly in pre-dialysis patients, although there still will be a degree of freedom for doctors to make their own decisions…In Europe, I think the dosage used would have been lower (than in the U.S.) anyway. So, perhaps there will be big changes in the doses used in the States. But I'm not convinced you'll see big changes in Europe because our practice was already slightly different."

ESA Use in Pre-dialysis Patients

ESA use in pre-dialysis patients is much less common in Europe than in the U.S., but where it is used in pre-dialysis patients, the cardiac safety issues do not appear to be chilling use. An Irish doctor said she will continue to use ESAs in pre-dialysis patients: "I would, in certain patients. It is very appropriate if they have a hemoglobin of 7 or 8 g/dL, and you want to avoid blood transfusions." A Czech doctor said, "I only use these agents in pre-dialysis patients in very rare cases."

Choice of ESA

Sources insisted that their choice of which ESA to use has not changed recently and has not been affected by the cardiac safety issue. An Italian nephrologist said, "We've maintained our use of (all three EPOs)." A U.K. doctor said, "There haven't been any changes that I'm aware. In the U.K., what you use is dependent upon regionally negotiated contracts." Another U.K. doctor said, "They (the government) give us a fixed budget, but otherwise it's up to us as to how we use these drugs." Another source said, "We are using these drugs in the same way we did before (the studies came out). And we are using the same agents. We have only EPO-alpha and EPO-beta in our country, and we use them mainly in dialysis patients. Only those 60 pre-dialysis patients involved in the Roche study are receiving EPO-beta. So mainly, it is dialysis patients who are on EPO therapy."

Outlook for Anemia Medications in Development

Several new brand-name anemia medications are in development, including:

➢ **Roche's Mircera (CERA).** Roche has gotten positive opinion from European regulators and is expected to be approved there soon. In the U.S., the FDA gave the company an approvable letter, with final approval expected after the Cardio-Renal Advisory Committee this fall. European nephrologists said they plan to try Mircera – if it is priced right.

- *U.K. #1:* "I suspect it will be reviewed when the contracts come up for renegotiation, but these EPO drugs are such a big part of the renal budget that (the choice) will depend on cost."
- *Macedonia:* "Maybe we will use it. As to whether we will use it instead of EPO-alpha or EPO-beta, depends on the price. I expect it will be a very expensive drug, and since these drugs are reimbursed under our government, the government won't pay for expensive drugs."

- *Ireland:* "I really don't know how much we might use it. We need more trials before we know where it'll fit."
- *Italy:* "You have the possibility of using the drug once a month, and this is of paramount importance, particularly for patients not on dialysis…In order to improve patient compliance and also well being – not to feel so much like an invalid – receiving the drug once a month is much better…(But use) depends on the price. I think by definition the competitor is darbepoetin, and, of course, the competition will be around the price. If CERA is around the same price or cheaper (than Aranesp), I'm sure that the extra benefit to have the possibility to reduce the frequency of dosing will make it very attractive."
- *Czech Republic:* "Definitely, we will use Mircera."
- *Switzerland:* "We have experience with all of the EPO agents, and we use them all in our unit. We are now going to try CERA and get some experience with it as well…But the other drugs (ESAs) work so well that I'm not sure what CERA's place will be…It could be better than the others, but whether it is, we really don't know. We have to see the side effects of CERA as well."
- *U.K. #2:* "I'm curious about the product, but I don't know much about it yet. However, if it's a monthly dose, it should be beneficial – the less frequent the dose, the less complex the regimen. If it's equally efficacious, and if it has the advantage of being given monthly, then I think it will be a better product."
- *Germany:* "I think it will be useful for patients. I can only speculate about how we'll use it, but I'm sure that doctors will use it when it's approved."
- *U.K. #3:* "I can absolutely see myself using it, mainly in pre-dialysis patients. And I would start new patients on Mircera, rather than replace an EPO agent for patients already on an ESA."

A poster at ERA-EDTA reported on the effect of iron status on hemoglobin stability in patients with CKD on once-monthly Mircera from a pooled analysis of two randomized, open-label, multicenter, parallel-group, Phase III trials (MAXIMA and PROTOS) of 832 patients (most of whom were on dialysis). The analysis found that patients with varying degrees of iron sufficiency could be successfully switched to IV or subcutaneous Mircera once-monthly and maintain stable hemoglobin levels.

Another poster reviewed the pharmacokinetics (PK) and stable maintenance of hemoglobin levels with once-monthly Mircera in CKD patients. In a pooled analysis of three Phase III trials (AMICUS, MAXIMA, and PROTOS), Mircera showed consistent and predictable PK and PD (pharmacodynamic) properties that remain stable with time and are not affected by route of administration (IV or subcutaneous) or frequency of administration (Q2W or Q4W).

➢ **AFFYMAX/TAKEDA'S Hematide.** Hematide, a synthetic peptide-based ESA, or EPO-mimetic, has finished Phase II trials and is expected to start a Phase III trial in 2H07, once the protocol details are worked out with the FDA. Dr. Locatelli said, "It offers the possibility of reducing the frequency of dosing. There are no problems with the production of antibodies (i.e., antibodies against EPO). Apparently, patients who have these kinds of complications respond very well to this drug, so this drug could be rescue therapy for these patients. It's an alternative…and I think it will be good."

A poster by Dr. Iain Macdougall et al reviewed the management of anemia in CKD with Hematide. In a 179-patient conversion and correction study, the researchers found:

- Hematide may be dosed Q4W in dialysis patients and CKD patients not on dialysis.
- Doses from 0.025-0.05 mg/kg are adequate to increase hemoglobin in anemic CKD patients.
- IV and subcutaneous dosing appear to result in similar hemoglobin increases, but dialysis patients require higher doses to maintain hemoglobin than non-dialysis patients.

➢ **FIBROGEN/ASTELLAS PHARMA'S FG-2216 (YM-311).** There was no new information at ERA-EDTA on this oral Hypoxia Inducible Factor (HIF) stabilizer, which was in Phase IIb trials in both dialysis and non-dialysis CKD patients as well as a Phase II trial in myelodysplastic syndrome. The trials were put on hold by the FDA in March 2007 after a pre-dialysis CKD patient in a Phase IIb trial died of fulminant hepatitis (acute liver failure). Astellas and FibroGen are investigating the death, but the definitive cause of this serious adverse event has not yet been established. Testing also was halted of another compound, FG-4592, which was in Phase IIa testing in the U.S. in pre-dialysis patients.

Asked about the outlook for FG-2216, Dr. Locatelli said, "This is important because it is an oral drug, and it has a completely different mechanism of action via hypoxia…There is a question mark about safety; there was one case of fulminant hepatitis. I don't think that the trial will be allowed to resume because any time there is a new drug with a complication like this, you have to be very cautious and stop the trial. But I have no idea about whether this death was related to the drug. Apparently, there was no relationship, but you never know. If this was the first drug for the treatment of anemia on the market, probably the trial would have been continued, but we have so many other drugs that you really need to be cautious because you really don't need another drug if it's not safe."

OUTLOOK FOR GENERIC ESAS

None of these sources is currently using any generic ESA, and none expressed much interest in generics, though price could drive use in the future. A German nephrologist said, "I'm aware that some centers use generic products, but in our center they are not used." ♦