

cell production in these patients and thus treat their anemia.

In the late 1980's, scientists used recombinant DNA technology to produce an erythropoietin-like protein called epoetin alfa. Epoetin alfa has exactly the same amino acid structure as the erythropoietin humans produce naturally and, when given to patients with anemia, stimulates red blood cell production.

Two commercial epoetin-alfa products are currently marketed in the United States: Epogen™ (marketed by Amgen) and Procrit™ (marketed by Ortho Biotech). These products are exactly the same but are marketed under two different trade names. Both Epogen™ and Procrit™ are approved by the FDA for marketing for the following conditions: (1) Treatment of anemia related to chronic renal failure (including patients on and not on dialysis), (2) treatment of Zidovudine-related anemia in HIV patients, (3) treatment of anemia in cancer patients on chemotherapy, and (4) treatment of anemia related to allogenic blood transfusions in surgery patients. Both products are given either intravenously or subcutaneously up to three times a week.

Amgen developed a new erythropoietin-like product, darbepoetin alfa, which it markets as Aranesp™. Also produced by recombinant DNA technology, darbepoetin alfa differs from epoetin alfa by the addition of two carbohydrate chains. The addition of these two carbohydrate chains affects the biologic half-life of the compound. This change, in turn, affects how often the biological can be administered, which yields a decreased dosing schedule for darbepoetin alfa by comparison to epoetin alfa. Amgen has received FDA approval to market Aranesp™ for treatment of anemia related to chronic renal failure (including patients on and not on dialysis) and for treatment of chemotherapy-related anemia in cancer patients.

Because darbepoetin alfa has two additional carbohydrate side-chains, it is not structurally identical to epoetin alfa. However, the two products use the same biological mechanism to produce the same clinical results—stimulation of the bone marrow to produce red blood cells.

These biologicals are dosed in different units. Epoetin alfa is dosed in Units per kilogram (U/kg) of patient weight and darbepoetin alfa in micrograms per kilogram (mcg/kg). The difference in dosing metric is due to changes in the accepted convention at the time of each product's development.

At the time epoetin alfa was developed, biologicals (such as those developed through recombinant DNA) were typically dosed in International Units (IU or Units for short), a measure of the product's biologic activity. They were not dosed by weight (for example, micrograms) because of a concern that weight might not accurately reflect their standard biologic activity. The biologic activity of such products can now be accurately predicted by weight, however, and manufacturers have begun specifying the doses of such biologicals by weight. No standard formula exists for converting amounts of a biologic dosed in Units to amounts of a drug dosed by weight.

In the clinical management of individual patients, CMS recognizes that no precise method of converting an epoetin alfa dose to a darbepoetin alfa dose has yet been established for any of the approved clinical uses. There are general guidelines for conversion and clinicians modify the dose based on the patient's hematopoietic response after the start of treatment with the new biological. For the purpose of developing a payment policy, however, it is feasible to establish a method of converting the dose of each of these drugs to the other. This payment methodology is intended to reflect average dosing requirements for the entire Medicare target population, and is not intended to serve as a guide for dosing individual patients.

As part of the process to define and further refine a payment conversion ratio between these biologicals, CMS held a series of meetings with representatives from both Amgen and Ortho Biotech. Both companies provided substantial new data, both published and unpublished. We also reviewed the Food and Drug Administration labeling for each product (Epogen™, Procrit™, and Aranesp™), hired an independent contractor to review the available clinical evidence, and performed an internal review of this evidence as well. CMS took into consideration both published and unpublished studies as well as abstracts, conference reports, clinical guidelines, marketing material, and other reports and materials provided by Amgen and Ortho Biotech.

As noted in the OPPS final rule for 2003, CMS was interested in having a "head-to-head" comparison of epoetin alfa to darbepoetin alfa either in patients with chronic kidney disease or in cancer patients with chemotherapy-induced anemia, and in which appropriate outcome measures were used. Because no head-to-head study has yet been completed, CMS also considered

clinical studies that either compared both products to each other or that linked the dose of a particular product with an appropriate health outcome measure. For the 2003 OPPS, we held a series of meetings with both Amgen and Ortho Biotech. We examined the written and published information provided by both companies, reviewed the FDA labeling for each product, hired an independent contractor to review available clinical evidence and performed an internal review of the evidence as well. In our review, we placed the greatest emphasis on published, high quality clinical studies and looked for the best possible estimates based on an evaluation of the dosing of each product that, on average, produced the same clinical response. Based on our own review of the evidence, our consultation with the independent contractor who also reviewed the evidence, and our discussions with each company, we established a conversion ratio for purposes of payment in 2003 of 260 International Units of epoetin alfa to one microgram of darbepoetin alfa (260:1).

Since publication of the OPPS final rule for 2003, we have continued to review and refine our analysis of the appropriate conversion ratio between these biologicals. In order to facilitate analysis of the non-peer reviewed materials submitted by Amgen and Ortho Biotech, we initiated a process in July 2003, in which each company shared with CMS, our contractor, and each other, a detailed description of the methods used in each of their unpublished clinical studies. Each company was then asked to submit to us their comments as well as the responses to questions raised by the other company's review. Finally, based on our analysis of this information, CMS submitted questions to each company to clarify their views. The final payment conversion ratio is based on our analysis of the information submitted during the process described above, as well as claims analysis, and other publicly available information.

*Chemotherapy-induced anemia:* The articles submitted by the manufacturers regarding treatment of chemotherapy-induced anemia (CIA) were all observational, retrospective, cohort studies. Several of these studies were conducted with a high degree of attention to minimizing avoidable bias and maximizing data integrity. Observational studies are, however, unavoidably subject to patient selection bias since study subjects are not randomly assigned to the groups being compared. It is not possible to eliminate the possibility that the choice of