

# Darbepoetin alfa (Aranesp)

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The Food and Drug Administration (FDA) approved darbepoetin alfa (Aranesp) for treatment of anemia associated with chronic renal failure (CRF) in patients on dialysis and patients not on dialysis (1). The manufacturer of the drug also filed an application with the FDA on September 18, 2001, to receive an indication for treatment of anemia in patients with cancer (Robert Hunter, Amgen Medical Affairs, personal communication, January 31, 2002). During development, the compound was called novel erythropoiesis stimulating protein, or NESP.

Anemia is defined as a reduction in hemoglobin or a reduction in the number of circulating red blood cells (2). Anemia has been further categorized by severity by several groups, including the National Cancer Institute and the World Health Organization (Table 1).

A normocytic, normochromic anemia is present in most patients with chronic renal disease and is usually observed when the glomerular filtration rate falls below 30 mL/min (5). Groopman and Itri reported that despite limitations in grading and reporting, the incidence of chemotherapy-related mild to moderate anemia in patients with cancer was relatively high. They explained that although historically such anemias have gone untreated, new data suggest that treatment results in significant improvements in quality of life measures for these patients (3).

## PRODUCT DESCRIPTION

Recombinant human erythropoietin (rHu-EPO) is a 30,400-Dalton, 165-amino-acid glycosylated protein hormone. The molecule is 60% amino acid and 40% carbohydrate by mass. The

carbohydrate portion of the molecule is found on 1 O-linked or 3 N-linked oligosaccharide chains. These chains are typically terminated with the negatively charged sugar molecule, sialic acid. As most other sugar molecules are neutral, the number of sialic acid residues is a significant determinant of the net negative charge of the molecule. Because of its structure, rHu-EPO can contain a maximum of 14 sialic acid residues (6).

Darbepoetin alfa differs from rHu-EPO in that it contains 5 N-linked oligosaccharide chains and has a molecular weight of 37,100 Daltons and a carbohydrate composition of 51%. These additional chains are accommodated by substitutions at 5 positions along the 165-amino-acid backbone, which do not alter the tertiary structure or its biologic activity. The additional carbohydrates result in longer half-life, increased biologic activity, and decreased receptor affinity (6).

## PHARMACOLOGY

Both rHu-EPO and darbepoetin alfa bind to the erythropoietin receptor on erythroid progenitor cells. Binding stimulates differentiation into mature red cells and inhibits apoptosis. In vitro, the affinity of the EPO receptor for darbepoetin alfa is less than that for rHu-EPO, but this does not translate into a loss of potency in vivo (7).

## PHARMACOKINETICS

As was found in animal models, darbepoetin alfa exhibits a half-life approximately 3 times longer than that of rHu-EPO when given as a single dose by the intravenous route in humans. With similar volumes of distribution, the extended half-life results in a significantly increased area under the curve (8) (Table 2).

The half-life of subcutaneously administered darbepoetin alfa has been reported to be between 2 and 3 times that of rHu-EPO, with other pharmacokinetic parameters being similar (9, 10). In another study designed to measure the pharmacokinetics of weekly subcutaneous injections of darbepoetin alfa at a dose of 2.25 µg/kg, the authors found a terminal half-life of 32.6 hours (standard deviation, 11.8) and a time to maximum concentra-

**Table 1. Classification of severity of anemia by hemoglobin level (g/dL)\***

Grade	National Cancer Institute†	World Health Organization‡
0	Normal limits	>11
1	10 to normal	9.5–10.9
2	8–10	8–9.4
3	6.5–7.9	6.5–7.9
4	<6.5	<6.5

\*The National Kidney Foundation suggests that an anemia workup be done for patients with chronic kidney disease when hemoglobin falls below 11 g/dL for women and below 12 g/dL for men (4).

†From reference 3.

‡From reference 4.

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**Table 2. Comparison of pharmacokinetic parameters for intravenous darbepoetin alfa and recombinant human erythropoietin\***

Parameter	Darbepoetin alfa (n = 11)	rHu-EPO (n = 10)
Terminal half-life (hr)	25.3 ± 2.2	8.5 ± 2.4
Clearance (mL/h per kg)	1.6 ± 0.3	4.0 ± 0.3
AUC <sub>(0-96 h)</sub> (ng·h per mL)	291.0 ± 7.6	131.9 ± 8.3
V <sub>d</sub> (mL/kg)	52.4 ± 2.0	48.7 ± 2.1

\*Adapted from reference 8. Results are given as mean ± standard error of the mean. rHu-EPO indicates recombinant human erythropoietin; AUC, area under the serum concentration–time curve; V<sub>d</sub>, volume of distribution at steady state.

tion of 86.1 hours (standard deviation, 22.8) (11). This compares with a half-life of approximately 19 hours of rHu-EPO in healthy volunteers receiving weekly injections of 750 U/kg (12).

### DOSING AND ADMINISTRATION

The approved dosage of darbepoetin alfa for anemia of CRF is 0.45 µg/kg given either intravenously or subcutaneously. Weekly monitoring of hemoglobin is suggested upon initiation of therapy and when the dosage is adjusted. Dosage should be adjusted to maintain hemoglobin levels <12 g/dL and to avoid increases of hemoglobin >1.0 g/dL over a 2-week period (10).

### ADVERSE EFFECTS

Comparing side effects from the package insert of darbepoetin alfa with those of rHu-EPO (Procrit and Epogen) reveals that the reported adverse reactions for Procrit and Epogen are identical. Adverse events reported in the darbepoetin alfa package insert appear different because of differences in standards when these products were studied and approved. In fact, when individual adverse effects can be matched, the 2 products are the same. The only difference is that darbepoetin alfa includes a greater number of adverse effects that are required by newer standards. In addition, the darbepoetin alfa adverse-effect profile is generated from experience with 1598 patients, whereas the Procrit/Epogen profiles are based on experience with only 200 patients (10, 12, 13).

In a study of 522 patients with end-stage renal disease who had previously received rHu-EPO, 347 were randomized to be switched to darbepoetin alfa. With 493 patients treated for 6 months and 103 treated up to 1 year, the investigators concluded that the adverse events and rates of withdrawals and deaths were similar in the darbepoetin alfa- and rHu-EPO-treated patient groups (14).

In another study of 703 patients on dialysis who were switched from rHu-EPO to darbepoetin alfa and monitored for 36 weeks, the authors concluded that the adverse-event profile of darbepoetin was similar to that of rHu-EPO (15).

In a pharmacokinetic study in patients with cancer, 16 patients received doses up to 4.5 µg/kg for a minimum of 6 weekly doses. The investigators indicated that darbepoetin alfa was well tolerated (16).

Darbepoetin alfa is contraindicated in patients with known hypersensitivity to the drug or any component of the formulation and in patients with uncontrolled hypertension (10).

### DRUG INTERACTIONS

No formal studies evaluating the interaction of darbepoetin alfa with other medications have been performed (10). Reports in the medical literature evaluating the potential interaction between angiotensin-converting enzyme inhibitors and rHu-EPO are conflicting (17). It is expected that darbepoetin alfa would have interactions similar to those found with rHu-EPO.

### DOSAGE FORMS

Darbepoetin alfa is currently available in 25-, 40-, 60-, 100-, and 200-µg single-dose vials. The FDA approved 2 formulations, but only the albumin formulation is currently available in the USA. The polysorbate formulation is forthcoming (Robert Hunter, Amgen Medical Affairs, personal communication, January 31, 2002).

### ECONOMIC ISSUES

Based on the actual peptide mass, 1 µg of darbepoetin alfa is equal to 200 U of rHu-EPO (9). Clinical equivalence is more difficult to determine. The manufacturer recommends starting darbepoetin alfa at a dose of 0.45 µg/kg once a week for patients with anemia associated with CRF (10). Procrit is suggested to be started at a dose of 50 to 100 U/kg 3 times weekly for patients with CRF who do not require dialysis (12). For patients with CRF who are on dialysis, Epogen should be started at a dose of 50 to 100 U/kg 3 times a week (13). A common regimen for comparing the 2 molecules in clinical trials was 0.45 µg/kg of darbepoetin alfa once weekly compared with 50 U/kg of rHu-EPO 2 times a week (9).

Because of the need for dosage titration with all of the agents in this class, direct comparison of cost is difficult. Current hospital acquisition costs for rHu-EPO products range from \$10.12 to \$10.80 per 1000 U and are \$3.63 per µg of darbepoetin alfa. A 70-kg patient treated once weekly with a dose of 0.45 µg/kg of darbepoetin alfa (31.5 µg) would require the use of one 40-µg vial at a cost of \$145.16. The same patient treated with a dose of 50 U/kg of Procrit (3500 U) would require three 4000-U vials, for a total cost of \$124.08. At the top end of the starting dosage range (100 U/kg), the 70-kg patient would require a dose of 7000 U of Procrit 3 times weekly. This could be accomplished by using one 3000-U vial and one 4000-U vial or using one 10,000-U vial for each injection. The respective weekly costs would be \$217.14 and \$303.69.

In addition to the actual drug costs, administration costs would be expected to be higher with rHu-EPO compared with darbepoetin alfa based on the actual number of injections that would be required. There is also the potential to have greater inventory cost with darbepoetin alfa based on the higher cost per unit.

### CLINICAL STUDIES

For the purposes of this article, 7 abstracts and 2 articles that describe original research comparing darbepoetin alfa with rHu-EPO in patients with CRF or cancer were reviewed (8, 9, 14, 15, 18–22) (Table 3). In addition, 3 abstracts and 3 articles that describe trials designed to determine pharmacokinetics, establish proper dosing, or establish efficacy were also reviewed (11, 16, 23–26). No difference was found in any of the studies that indi-

Table 3. Review of selected literature on darbepoetin alfa

Reference	Population	Drug/control regimen	Methods	Parameters monitored	Results and conclusion
Locatelli et al, 2001 (9)	RHu-EPO naïve CRI patients (n = 166)	NESP 0.45 µg/kg SC weekly; rHu-EPO 50 U/kg twice weekly	3:1 randomization NESP:rHu-EPO	Hgb levels	93% and 92% of NESP and rHu-EPO patients achieved and maintained Hgb levels of 11–13 g/dL over 24-week study period.
Vanrenterghem et al, 1999 (14)	HD and PD patients maintained on 1–3 weekly doses of rHu-EPO with baseline Hgb of 9.5–12.5 g/dL (n = 522)	Randomized to continue rHu-EPO (n = 175), weekly NESP by same route (n = 281), or NESP every other week (n = 66). Study period was up to 52 weeks.	1:2 randomization rHu-EPO:NESP	Hgb levels	Baseline Hgb of 9.5–12.5 g/dL was maintained within –1.0 to +1.5 g/dL and 95% in 97% of weekly and every-other-week NESP regimens.
Graf et al, 2000 (15)	HD and PD patients maintained on 1–3 weekly doses of rHu-EPO with baseline Hgb of 9.5–12.5g/dL (n = 703)	Patients on 1 weekly dose rHu-EPO were switched to every-other-week NESP (n = 157), and patients on 2–3 weekly doses of rHu-EPO were switched to weekly NESP (n = 546). Study period was 36 weeks.	Nonrandomized one-way crossover	Hgb levels	Baseline Hgb of 9.5–12.5 g/dL was maintained within –1.0 to +1.5 g/dL in 96% of all patients and 89% of every-other-week patients. Mean Hgb change was –0.08 g/dL from baseline to week 36.
Coyne et al, 2000 (22)	CRF patients receiving dialysis with anemia defined as Hgb ≤10 g/dL and who had not received rHu-EPO within 12 weeks of enrolling in the study	Patients were randomized in a 3:1 fashion to receive NESP at a dose of 0.45 µg/kg/week or 50 U/kg rHu-EPO 3 times per week for a study period of 20 weeks. Doses were administered by SC or IV routes. Dosage adjustments were performed in an unspecified manner.	Randomized; blinding not specified	Hgb concentration	Change from baseline Hgb was +1.10 and +1.33 for the NESP and rHu-EPO groups. 72% and 84% of NESP and rHu-EPO patients achieved target Hgb concentration (≤11 g/dL). At the end of the study, the median weekly dose for NESP was 0.56 µg/kg/week and 156 U/kg/week for rHu-EPO.
Glaspay et al, 2001 (25)	Solid tumor patients receiving multicycle chemotherapy for up to 12 weeks with baseline anemia defined as Hgb levels <11 g/dL	Three cohorts of escalating doses of darbepoetin: 0.5 µg/kg/week (n = 13), 1.5 µg/kg/week (n = 35), and 2.25 µg/kg/week (n = 59). All doses were given as a single SC injection.	Sequential, nonblinded dose-escalation study	Hgb change from baseline	The 0.5, 1.5, and 2.25 µg/kg/week dosages produced increases in hemoglobin of 1.24, 1.73, and 2.15 g/dL, respectively, at the end of the 16-week study period.

rHu-EPO indicates recombinant human erythropoietin; CRI, chronic renal insufficiency; NESP, novel erythropoiesis stimulating protein; SC, subcutaneous; Hgb, hemoglobin; HD, hemodialysis; PD, peritoneal dialysis; CRF, chronic renal failure; IV, intravenous.

cated a direct clinical advantage to either product. The only benefit seen with darbepoetin alfa was the convenient dosing interval (2–3 times longer than with rHu-EPO). This may translate to improved compliance in an outpatient setting but must be weighed against length of stay in the inpatient hospital setting. Administration of darbepoetin during a short hospital stay would result in disproportionately higher drug costs to the institution compared with those for using rHu-EPO.

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