

Bon Secours Richmond
Pharmacy & Therapeutics Committees
Epoetin and Darbepoetin
6/2002

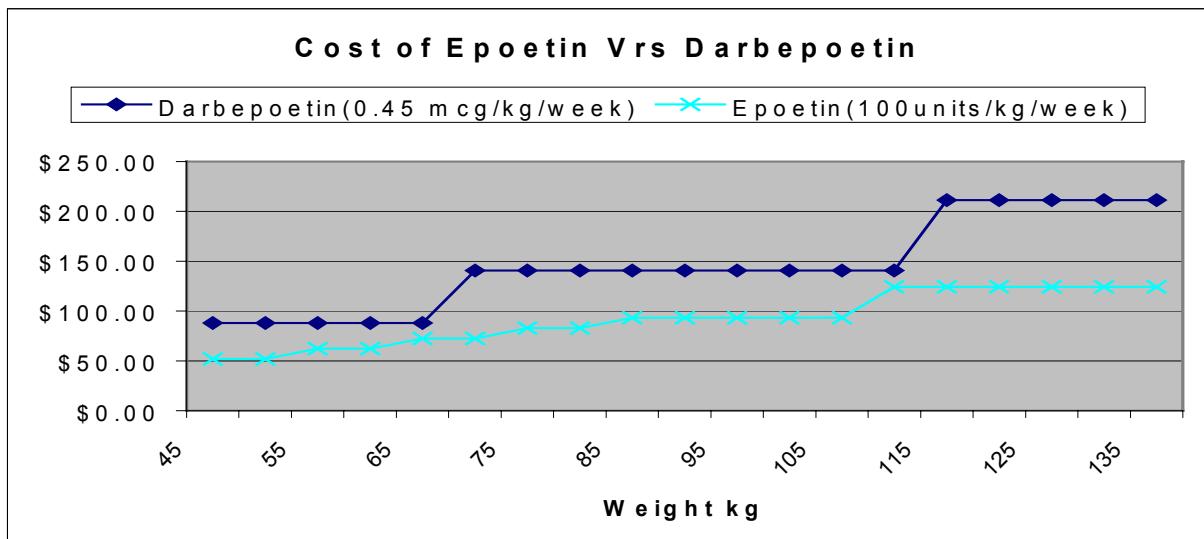
Recommendations: MEC Approved at MPMC/RCH/SMH

- Darbepoetin (Aranesp™) is not recommended for addition to formulary as it is fifty-eight percent more expensive than an equivalent dose of epoetin and offers no advantage to the hospitalized patient.
- An automatic substitution of epoetin using a conversion of 100 units/kg/week of epoetin for 0.45 mcg/kg/week of darbepoetin is recommend. *Patients receiving darbepoetin every other week will be given weekly epoetin. Patients receiving darbepoetin every week will receive epoetin two to three times a week.*

Findings:

- Darbepoetin is an erythropoiesis stimulating protein and differs from epoetin by having 5 N-linked oligosaccharide chains versus 3 in epoetin. This change increases the half-life allowing less frequent dosing and does not interfere with receptor binding.
- Darbepoetin demonstrates linear kinetics/dose proportionality.
- Darbepoetin 0.45 mcg/kg/week is equivalent to 100 units/kg/week of epoetin.
- No differences have been show between darbepoetin and epoetin in: mean increase in Hgb, % of patients reaching target Hgb, and mean time to achieve target Hgb levels for equivalent doses.
- The dosage equivalence chart in the package insert of darbepoetin (Aranesp™) underestimates the potency of epoetin. Equivalent doses in studies were 1 mcg/kg/week darbepoetin = 200 units/kg/week of epoetin or 0.45 mcg/kg/week of darbepoetin = 100 units/kg/week of epoetin. The ratio in the package insert is 1 mcg/kg/week = 300 to 515 units/kg/week. Leading to an overestimate of the cost of epoetin when compared to darbepoetin.

Dosage Equivalence					
Darbepoetin mcg/week	25	40	60	100	200
Darbepoetin Cost	\$88	\$141	\$211	\$352	\$704
Epoetin units/week	6,000	8,000-9,000	12,000-14,000	20,000	40,000
Epoetin Dosing Schedules	6,000 units 1 x/wk 3,000 units 2 x/wk	8,000 units 1 x/wk 4,000 units 2 x/wk 3,000 units 3 x/wk	14,000 unit 1 x/wk 6,000 units 2 x/wk 4,000 units 3 x/wk	20,000 units 1 x/wk 10,000 units 2 x/wk 7,000 units 3 x/wk	40,000 units 1 x/wk 20,000 units 2 x/wk 14,000 units 3 x/wk
Epoetin Cost	\$52	\$83-93	\$124-143	\$203	\$406



Studies:

De Novo Use in Patients with Chronic Renal Failure

Darbepoetin alfa was compared with epoetin in 121 patients undergoing dialysis and with a baseline Hgb value ≤ 10 g/dL who had not received epoetin in the previous 12 weeks. Patients were treated with darbepoetin alfa 0.45 mcg/kg once weekly or epoetin 50 units/kg three times weekly. The darbepoetin alfa dose was approximately equivalent to 90 units/kg of epoetin weekly based on peptide mass. Therapy was administered IV or SC for 20 weeks. Dosage adjustments were permitted as necessary to achieve a target Hgb 11-13 g/dL. The mean increase in Hgb over the first 4 weeks of therapy was 1.1 g/dL in the darbepoetin alfa group and 1.33 g/dL in the epoetin group. Target Hgb levels were achieved during the study in 72% (95% CI: 62%, 81%) of 90 darbepoetin alfa-treated patients and 84% (95% CI: 66%, 95%) of 31 epoetin-treated patients. The median time to achieve target Hgb levels was 10 weeks in the darbepoetin alfa group and 8 weeks in the epoetin group. The median weekly dose at week-20 was 0.56 mcg/kg for darbepoetin alfa and 156 units/kg for epoetin.^{1,20}

In another similar study, 166 patients with chronic renal insufficiency not requiring dialysis and baseline Hgb levels < 11 g/dL who had not received epoetin in the past 12 weeks were treated with either darbepoetin alfa 0.45 mcg/kg once weekly SC or epoetin 50 units/kg twice weekly SC. Patients also had to have a serum ferritin < 100 mcg/L, serum vitamin B₁₂ and folate levels above the lower limit of normal, and a creatinine clearance of < 30 mL/min. Red blood cell transfusions or androgen therapy could not have been used within 8 weeks of administration of the first dose of the study medication. Patients were excluded from the study if they had uncontrolled hypertension, congestive heart failure (New York Heart Association Class III or IV), anemia caused by a hematologic disorder, systemic infection or inflammatory disease, or other conditions that could interfere with the response to erythropoietin. The patients were not equally randomized to darbepoetin alfa and epoetin therapy, instead a 3:1 ratio was used. Therapy was continued for 24 weeks. Dosage adjustments were made as needed to achieve the targeted Hgb response of an increase of ≥ 1 g/dL from baseline and a Hgb concentration of 11 to 13 g/dL. The majority of these patients in both groups were white (darbepoetin alfa 95% and epoetin 97%), and the average age of both groups was ~ 60 years. The cause of renal failure was generally similar and the baseline hemoglobin was 9.3 g/dL and 9.8 g/dL, serum ferritin was 168 mcg/L and 151 mcg/L, and creatinine clearance was 15.7 mL/min and 15.7 mL/min, respectively. The mean increase in Hgb over the first 4 weeks of therapy was 1.38 g/dL (95% CI, 1.21 to 1.55) in the darbepoetin alfa group and 1.4 g/dL (95% CI, 1.07 to 1.27) in the epoetin group. Target Hgb levels were achieved during the study in 93% (95% CI: 87%, 97%) of 129 darbepoetin alfa-treated patients and 92% (95% CI: 78%, 98%) of 37 epoetin-treated patients. An increase in hemoglobin of 1 g/dL or greater was achieved in 99% (95% CI, 96% to 100%) of darbepoetin alfa-treated patients and 95% (95% CI, 82% to 99%) of epoetin-treated patients. The median time to achieve target Hgb levels was 7 weeks in both groups (range 3 to 25 weeks). At the time of Hgb response, the median weekly dose was 0.46 mcg/kg (range 0.3-2.3 mcg/kg) for darbepoetin alfa and 100 units/kg (range 75-175 units/kg) for epoetin. At week-24, the median weekly dose was 0.34 mcg/kg (range 0-1.3 mcg/kg) for darbepoetin alfa and 56.9 units/kg (range 19-250 units/kg) for epoetin.^{1,21,22}

Conversion from Epoetin in Patients with Chronic Renal Failure

In a double-blind study, 507 hemodialysis patients were randomized to therapy with darbepoetin alfa administered IV once weekly plus placebo twice weekly (169 patients) or to continue to receive epoetin IV three times weekly (338 patients) in a 28-week study with a 20-week dose-titration period and an 8-week evaluation period. Dosages were adjusted as needed to maintain Hgb concentrations within -1 and +1.5 g/dL of their mean baseline Hgb value and between 9 to 13 g/dL for up to 28 weeks. The median weekly darbepoetin alfa dose was 0.53 mcg/kg. The mean change in Hgb between baseline and the evaluation period was 0.16 g/dL for darbepoetin alfa. No change was observed in the patients that remained on epoetin. The frequency of dose changes was similar in both groups, as was the percentage of patients with Hgb concentrations defined as unstable (35% with darbepoetin alfa and 38% with epoetin). Overall, safety and efficacy appeared comparable.^{1,26}

In another similar study, 522 patients on hemodialysis or peritoneal dialysis and with baseline Hgb between 9.5 to 12.5 g/dL on epoetin therapy were either switched to darbepoetin alfa therapy or maintained on epoetin therapy at the same dose, frequency, and route. Patients receiving epoetin once weekly (n=101) were switched to darbepoetin alfa once every other week. Patients receiving epoetin two (n=177) or three (n=244) times weekly were switched to darbepoetin alfa once weekly. Darbepoetin alfa was administered by the same route as epoetin had been and was initially dosed at an equivalent dose. The darbepoetin alfa and epoetin doses were subsequently adjusted to maintain Hgb within -1 to +1.5 g/dL of the baseline Hgb and within a range of 9 to 13 g/dL for up to 52 weeks. The median weekly darbepoetin alfa dose was 0.41 mcg/kg. The mean change in Hgb from baseline to evaluation between weeks-24 and -32 was -0.03 g/dL in the darbepoetin alfa group and -0.06 g/dL in the epoetin group. At the end of the evaluation period, 97% of patients treated with darbepoetin alfa once a week and 95% treated with darbepoetin alfa once every other week were maintained at these dose frequencies.^{1,27}

In a similar study, 703 patients on hemodialysis or peritoneal dialysis and with baseline Hgb between 9.5 to 12.5 g/dL on epoetin therapy were switched to darbepoetin alfa therapy. Patients receiving epoetin once weekly (n=157) were switched to darbepoetin alfa once every other week. Patients receiving epoetin two (n=203) or three (n=343) times weekly were switched to darbepoetin alfa once weekly. Darbepoetin alfa was administered by the same route as epoetin had been and was initially dosed at an equivalent dose (200 units epoetin = 1 mcg darbepoetin alfa). The darbepoetin alfa dose was adjusted to maintain Hgb within -1 to +1.5 g/dL of the baseline Hgb and within a range of 9 to 13 g/dL. The mean change in Hgb from baseline to week-36 was -0.08 g/dL. The median darbepoetin alfa dose was equivalent to the weekly epoetin dose at study entry.²⁸