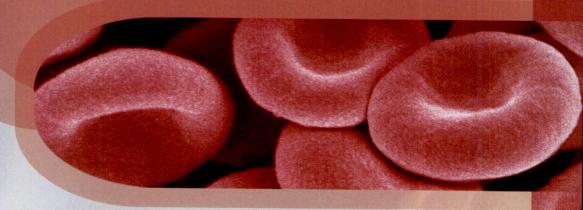# Optimizing Erythropoietic Growth Factor Formulary Management: Interchange Opportunities

Erythropoietic Growth Factors: Budgetary Impact

Erythropoietic growth factors (EGFs) have a significant impact on the budgets of health systems, consistently ranking as one of the highest annual drug expenditures. In 2003, blood growth factors (including the EGFs and colony-stimulating factors [CSFs]) were ranked as the third highest expenditure for nonfederal hospitals, at nearly $2.4 billion. This was an increase of 11% from the previous year. Together, the top 10 therapeutic drug classes accounted for more than 70% of the hospitals' drug expenditures for that year.[1]

Looking at specific drugs from the inpatient perspective, 3 growth factors ranked among the top 15 highest drug expenditures in 2003: epoetin (#1, $1.4 billion), filgrastim (#8, $344 million), and pegfilgrastim (#11, $296 million). Similarly, in the outpatient setting, epoetin, pegfilgrastim, and darbepoetin ranked #1, #4, and #5, respectively, among the top expenditures for 2003. More than $5.3 billion was spent on these 3 growth factors in 2003.[1]

Centers for Medicare & Medicaid Services (CMS) reimbursement for the EGFs has steadily decreased from 2004 through the present time. This will have a substantial impact on oncology practices, which face diminishing revenues. It is expected that these changes to Medicare reimbursement will force the physician offices to send their patients to outpatient hospital clinics. Hospital clinics must be prepared for this expected shift in growth factor use (both EGFs and CSFs). The most cost-effective approach for health systems is to use 1 EGF in both the outpatient clinic and inpatient settings. This can be accomplished by the use of therapeutic interchange (TI).

Therapeutic Interchange Process

As mentioned, EGF usage and expenditures continue to increase and remain a substantial budgetary concern. Additionally, the expected influx of patients from physicians' offices has intensified the need for health systems to critically evaluate their formularies and include only the most cost-effective medications. TI is an efficient means for a healthcare organization to maintain quality patient care while controlling cost. Unlike generic substitution, where one drug is used in place of another chemically identical and bioequivalent

drug, TI refers to the interchange of therapeutically equivalent but chemically distinct drugs within a healthcare organization's evidence-based formulary. A TI must be based on valid clinical evidence and subjected to a rigorous review process by the organization's Pharmacy & Therapeutics (P&T) Committee.

A proper TI program begins with a thorough evaluation of all medications being considered. This involves a review of the medical literature to ensure the drugs are therapeutically equivalent. Supportive clinical evidence must be available to establish equivalent efficacy, safety, and durability. Additionally, cost or other advantages such as increased dosing interval administration time or improved patient quality-of-life must be considered.[2]

Various healthcare organizations have taken a position on TI. Pharmacy organizations, such as the American Society of Health-System Pharmacists (ASHP), the American College of Clinical Pharmacy (ACCP), and the Academy of Managed Care Pharmacy (AMCP) support TI, as long as the program is appropriately designed and implemented. Both ASHP and ACCP specify that the development of the TI should involve a collaborative effort between pharmacists and prescribers/physicians.[2] The American Medical Association (AMA) only approves TI when numerous specific conditions are met, including physician approval of all P&T Committee recommendations and protocols for informing individual physicians. The AMA opposes TI without prior authorization, and requires that the prescriber have the ability to override the TI on an individual patient basis, without excessive administrative obstacles.[3]

Development and implementation of a TI involves 6 essential criteria that ensure the provision of safe and effective pharmaceutical care, as well as a successful program.[2,4] A proposed TI program must meet the following 6 criteria:

Pharmacologic equivalence

Drugs being considered for a TI must produce equivalent therapeutic effects, with similar pharmacokinetic and pharmacodynamic profiles. They must produce comparable clinical outcomes, in terms of therapeutic beneficial effects, and should have comparable adverse-event profiles.

Clinical evidence

Above all, a TI must be based on appropriate, well-conducted clinical trials. Ideally, head-to-head clinical data should be reviewed, but such trials are not always available. The drugs under consideration for the TI must demonstrate equivalent safety and efficacy, in both the short and long term, for each indication. Although indication-specific TIs are implemented in some institutions, this practice is much more difficult to administer and may significantly increase the risk for medication errors.

Cost or other advantages

The goal of any TI is to have a neutral or positive effect on patient outcome while reducing the organization's overall costs. A comparative evaluation of drug cost must employ the appropriate pharmacoeconomic model, such as cost minimization, cost benefit, or cost-effectiveness. It is important not to limit the analysis solely to drug acquisition cost, but also to consider indirect costs (eg, cost per day of hospitalization, cost of treating adverse events, cost of monitoring), since these contribute to the total cost of therapy.

Other potential advantages of one drug over another include decreased length of stay, reduced administration time, increased patient compliance, or improved quality of life.

Pharmacy & Therapeutics Committee evaluation

An appropriate P&T Committee evaluation of a TI includes several criteria: 1) a thorough, balanced analysis of all published clinical data; 2) the development of all necessary policies and procedures; 3) the development of an educational program for all involved healthcare personnel, including physicians, nurses, and pharmacists; 4) the development of a means

of documentation in patients' records each time the TI is instituted; and 5) the establishment of ongoing communication with all involved healthcare personnel.

Opportunity for variance

Prescribers should be able to override the TI on an individual patient basis without undue or overrestrictive administrative requirements.

Monitoring of outcomes

Once established, there should be a means for monitoring patient outcomes. The TI should include a plan for evaluation of safety, efficacy, cost, and patient satisfaction.

The development of an EGF TI is an excellent example to illustrate the proper use of these 6 criteria.

Erythropoietic Growth Factors: Clinical Evidence and Therapeutic Equivalence

The initial step of any TI is a review of the clinical evidence to determine if the drugs under consideration are therapeutically equivalent. In this case, all indications of the EGFs must be evaluated: oncology-associated anemia, anemia of chronic kidney disease (CKD) (both dialysis and nondialysis patients), and other indications, such as myelodysplastic syndrome and critical care.

Oncology-associated anemia

One of the primary indications for the EGFs is oncology-associated anemia. The standard of practice today is the weekly administration of epoetin and biweekly administration of darbepoetin, based on the following studies:

In the Gabrilove study, 2964 patients received an initial epoetin dose of 40,000 units weekly, resulting in a hematopoietic response rate of 68%.[5] Response rate was defined as an increase in hemoglobin (Hb) of >2 g/dL from baseline and/or an Hb level of 12 g/dL or greater. At 4 weeks, if the Hb did not increase by at least 1 g/dL, the dosage was increased to 60,000 units once weekly, at the physician's discretion. In this study, approximately one-third (33%) of patients were given such a dosage escalation.[5]

One limitation of this study is that the study results were not adjusted for transfusion. Since a transfusion affects Hb quicker than a growth factor does, it masks the need for dosage escalation. This may cause the escalation rate to be artificially low. Additionally, data analysis occurred via "completer" methodology, which includes only the patients who finished the study in the final results, not the entire cohort; this may skew the results in a more positive direction.

The SOAR (Successful Outcomes in Anemia Research) study treated 1173 patients with darbepoetin 3 mcg/kg every 2 weeks. Dosage escalation to 5 mcg/kg was mandated, according to the same criteria as the Gabrilove trial. However, unlike the Gabrilove study, data were evaluated using an intent-to-treat analysis, and adjusted for transfusions. In this trial, 43% of patients required dose escalation. The hematopoietic response rate was 84%.[6,7]

The SURPASS (Study to Understand and Reduce Patient Anemia and Symptom Severity) study utilized darbepoetin 200 mcg every 2 weeks (Q2W), with escalation to 300 mcg Q2W if needed for an inadequate Hb response (Hb increase 1 g/dL at Week 5). An intent-to-treat analysis of 2026 patients revealed a hematopoietic response rate of 72%.[8]

Several head-to-head studies have also been performed comparing darbepoetin 200 mcg Q2W with epoetin 40,000 units every week (QW) among anemic oncology patients. Waltzman and colleagues allowed different dose-escalation time frames: 4 weeks for epoetin and 6 weeks for darbepoetin. The 2 most common tumor types were in the breast and lung. The primary end point was the Hb response rate, which excluded Hb values within 4 weeks of a transfusion. An interim analysis, performed after 305 patients had completed 4 weeks of therapy, showed a statistically significant higher response rate for epoetin (47%) than for darbepoetin (33%), P=.0078. (In this study, "response" was defined as an increase in Hb of 1 g/dL or greater at 4 weeks.[9])

Several issues with this study include: 1) these results are inconsistent with larger randomized controlled trials and medication usage evaluation (MUE) data, which demonstrated similar results with epoetin and darbepoetin; 2) the analysis was performed at 4

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weeks, before the darbepoetin group was given the opportunity to have a dosage escalation; and 3) patient numbers were not defined for study end responsiveness.

Schwartzberg and colleagues used the same regimens in patients with breast, lung, or gynecologic cancer; both regimens allowed dosage escalation after 4 weeks. This study showed that the 2 drugs performed equally well in achieving and maintaining a Hb 11 g/dL, within each tumor type and in the combined analysis. At 17 weeks, the mean change in Hb from baseline was 1.4 g/dL for darbepoetin and 1.5 g/dL for epoetin (P=.352). The mean time to reach the target Hb of 11 g/dL or greater was similar, at 5 weeks for darbepoetin and 4 weeks for epoetin.[10]

Glaspy and colleagues conducted a larger, multicenter, randomized, head-to-head trial comparing darbepoetin 200 mcg Q2W (n=606) with epoetin 40,000 units QW (n=603). The primary end point was the transfusion requirement from Day 29 through the end of treatment (up to 16 weeks). The secondary end point was achieving a target Hb of 11 to 13 g/dL. The transfusion requirement was 21% for darbepoetin patients and 16% for epoetin patients, which represented non-inferiority between the 2 EGF regimens.[11] Table 1 illustrates other pertinent results.

Table 1. Head-to-head Trial Results

	Darbepoetin (n=606)	Epoetin (n=603)
Patients achieving Hb target (11–13 g/dL)	76%	81%
Median time to Hb target	6 weeks	5 weeks
Patients maintaining Hb target at Week 17	74% (n=438)	80% (n=470)

These head-to-head studies have further established the therapeutic equivalence of epoetin and darbepoetin in the management of oncology-associated anemia, as well as the standard of practice regimens: epoetin 40,000 units QW and darbepoetin 200 mcg Q2W.

In addition to standard-of-practice dosing, extended dosage intervals are being investigated for both epoetin and darbepoetin. It is postulated that a higher starting dose of an EGF, followed by less frequent maintenance dosing, might shorten the time to Hb response and increase response rates. One study initiated epoetin at 60,000 units weekly until the Hb rose to 12 g/dL or higher, then switched patients to a maintenance phase of 80,000 units every 3 weeks (Q3W). Overall, 61% of patients achieved an Hb of 12 g/dL or an increase of 2 g/dL from baseline; however, the small number of evaluable patients (n=36) limits the applicability of these results.[12]

Two studies of darbepoetin 300 mcg Q3W have been reported. One compared "early" intervention (n=99), where darbepoetin was begun when the Hb was 10.5 to 12 g/dL, with "late" intervention (n=102), where darbepoetin was not started until the Hb was 10 g/dL or lower. Greater than 90% of patients in both groups maintained or achieved a target Hb of 11 g/dL or higher. Early initiation was associated with a significantly lower likelihood of the Hb dropping below 10 g/dL and significantly fewer transfusions.[13] A much larger trial (n=1225) has provided more definitive data regarding the efficacy of darbepoetin 300 mcg Q3W. Patients were grouped according to their baseline Hb: <10 or ≥10 g/dL; the target Hb (11–12 g/dL) was achieved in 89% and 92% of the 2 groups, respectively.[14]

These studies indicate that Q3W EGF administration, particularly with darbepoetin, may be an effective and convenient alternative dosing regimen. This would facilitate synchronized dosing with chemotherapy, since many chemotherapeutic regimens are administered on a Q3W schedule.

Anemia of chronic kidney disease

The second major indication for the EGFs is the management of anemia associated with CKD. Table 2 (page 7) presents typical current standard-of-practice regimens for EGFs in CKD, based on current literature.[15-19] Dialysis patients generally require higher weekly EGF doses with a more frequent administration schedule than nondialysis patients.

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Evolving regimens of both EGFs are being studied and are being used in practice: epoetin 10,000 units once weekly and darbepoetin at a Q2W interval. Studies have been reported demonstrating that extended dosing intervals of both epoetin and darbepoetin in CKD are effective in maintaining Hb.

Table 2. EGF Standard-of-practice Dosing in CKD

	Epoetin	Darbepoetin
Dialysis	20–120 units/kg divided TIW	40–60 mcg QW
Nondialysis	7000 units QW	50–60 mcg Q2W

TIW=3 times per week.

Chronic Kidney Disease Dialysis

A key study that established the therapeutic equivalence of darbepoetin and epoetin among CKD patients on dialysis took patients stabilized on epoetin and randomized them in a 1:2 ratio to continue their current epoetin regimen or be converted to darbepoetin. Conversion occurred in the following manner: epoetin twice or 3 times weekly was converted to darbepoetin weekly; epoetin once weekly was converted to darbepoetin Q2W. The dosage conversion ratio was 200 IU epoetin to 1 mcg darbepoetin, which was adjusted to maintain Hb within the range of –1 to +1.5 g/dL of their baseline Hb and between 9 to 13 g/dL for the 52-week study period.[20]

A total of 519 patients were included in the intent-to-treat analysis. The mean weekly Hb values for the darbepoetin and epoetin groups were not significantly different throughout the study. The mean change in Hb from baseline to evaluation was –0.03 g/dL (standard error [SE]=0.11) for the darbepoetin group and –0.06 g/dL (SE=0.13) for the epoetin group. At the end of the evaluation period, ≥95% of patients successfully maintained their Hb on their assigned dose frequency for both drugs, with similar safety profiles. Thus, this noninferiority trial demonstrated that darbepoetin was just as effective as epoetin in maintaining Hb among dialysis patients, even at a reduced administration frequency.[20]

A retrospective review of a therapeutic interchange program was conducted with 145 dialysis patients maintained on epoetin in the outpatient setting prior to hospitalization. At admission, patients were converted to epoetin using the conversion ratio cited in the product information (200 international units epoetin=1 mcg darbepoetin). Another 99 patients maintained on epoetin throughout their hospitalizations served as historical controls. At study start, there was minimal difference in the mean Hb between groups: 12.2 g/dL for the darbepoetin group and 11.8 g/dL in the epoetin group (P=.14). The mean length of stay was 8.1 days for the darbepoetin group and 8.4 days for the epoetin group. Upon discharge, the mean Hb was identical for both groups: 11.4 g/dL. This therapeutic interchange was effective in the management of anemia in hospitalized dialysis patients.[21]

Chronic Kidney Disease Nondialysis

Three studies support the use of darbepoetin Q2W in patients with CKD who are not maintained on dialysis. Two of these studies evaluated the efficacy of darbepoetin 0.75 mcg/kg Q2W among epoetin-naïve patients. An Hb response, defined as a final Hb of 11–13 g/dL, was achieved in 95% and 97% of patients, with a median time-to-response of 5.7 and 5 weeks, respectively.[17,22] The third study evaluated darbepoetin 0.75 mcg/kg administered Q2W to 1426 patients who were either epoetin-naïve or previously managed on epoetin administered weekly. An interim analysis of 1103 patients at 21 to 24 weeks found that darbepoetin maintained Hb levels (10–12 g/dL) in both epoetin-naïve and converted groups, 96.4% and 98%, respectively.[23] These 3 studies demonstrated that darbepoetin administered Q2W maintained target Hb levels in CKD nondialysis patients who were either naïve to epoetin or converted from stable epoetin therapy.

Evolving dosing strategies in CKD patients not on dialysis have incorporated prolonged dosing intervals. Two clinical trials have been performed to date. The first trial evaluated the efficacy and safety of extending the darbepoetin dosing interval from Q2W to once every month (QM), using an initial dose of twice the Q2W dose, and adjusted thereafter to maintain a Hb of 10 to 12 g/dL. Table 3 illustrates the baseline values with Q2W darbepoetin dosing compared with the evaluation point with once-monthly dosing.[24]

Hb was maintained within target range in 79% of patients, according to intent-to-treat analysis, and the safety profiles for the 2 regimens were similar. Extending the darbepoetin Q2W dose to QM effectively and safely maintained target Hb levels.[24]

Table 3. Study of Monthly Darbepoetin Dosing in CKD

	Baseline	Evaluation Point (21–29 weeks)
Hb	11.1 g/dL	11.0 g/dL
Mean monthly darbepoetin dose	88.7 mcg	86.6 mcg

The second study randomized patients stabilized on epoetin therapy for ≥2 months (Hb ≥11 g/dL) to 1 of 4 epoetin regimens: 10,000 units QW, 20,000 units Q2W, 30,000 units Q3W, and 40,000 units QM. Mean baseline Hb levels (11.9 g/dL) and glomerular filtration rate (20.7 mL/min/1.73 m^2) were similar between groups. The primary end point was the mean final Hb for each group after 16 weeks. All groups had a mean final Hb ≥11 g/dL; however, only the Q2W and QM groups met the protocol-defined criteria for equivalence to the QW group. No differences in safety between groups were found. This study demonstrated that QW, Q2W, and QM epoetin regimens maintained target Hb levels.[25]

Other indications

Two other indications with a growing amount of clinical evidence are the management of anemia from myelodysplastic syndrome (MDS) and among critical care patients.

MDS is a hematopoietic stem cell disorder characterized by anemia and varying types of cell dysplasia; it is typically managed with chemotherapy and/or EGFs. Patton and colleagues performed a retrospective cohort study of 263 MDS patient charts to evaluate the effects of a TI of darbepoetin for epoetin. Seventy-seven patients were switched from their current regimen of epoetin to darbepoetin 200 mcg Q2W. Their results were compared with a cohort of 60 patients maintained on epoetin, following 16 weeks of therapy.[26]

At baseline, both groups had a similar mean Hb level: 11 g/dL for the darbepoetin group and 11.2 g/dL for the epoetin group. After 16 weeks, an intent-to-treat analysis was performed. Patients switched from epoetin to darbepoetin had a 26% major response (increase in Hb of 2 g/dL over baseline or no transfusions), compared with 17% for the patients who had been maintained on epoetin. The minor response rate (Hb increase of ≥1 g/dL to <2 g/dL, or a 50% decrease in transfusions) was identical for both groups (25%). This analysis demonstrated equivalent efficacy of darbepoetin and epoetin in patients with MDS.[26]

When considering critically ill patients, nearly 95% of all intensive care unit patients are anemic, with an Hb below normal by Day 3. Some causes include phlebotomy (for continual laboratory assessment); bleeding from trauma, surgery, and other sources; a blunted erythropoietic response; and a decrease in circulating iron. Many patients have underlying disease states, such as CKD or cancer. As a result, 14% of critically ill patients in the United States are transfused daily. There are many issues associated with blood transfusions, including shortages and the potential for adverse reactions or infection. Additionally, transfused red blood cells (RBCs) do not function as the patient's own RBCs do, because with storage they lose their oxygen unloading capacity and have a shorter lifespan. Finally, there is some evidence linking blood transfusions to a lower survival rate. One study found that patients treated with a liberal transfusion policy (transfusion at 9 g/dL) had a lower survival rate (death rate at 30 days, 23.3%) than those with a restrictive policy (transfusion at 7 g/dL; death rate at 30 d, 18.7%).[27]

It would seem that a viable alternative to transfusion in the critically ill patient would be an EGF. However, EGF use in this setting has been questioned because of the limited amount of evidence. Only 1 prospective randomized trial has been performed comparing epoetin 40,000 units (n=650) with placebo (n=652) weekly for a total of 3 doses. Significantly fewer patients treated with epoetin (50.5%) than those given placebo (60.4%) required a transfusion (P<.001). Additionally, there was a 19% decrease in the number of units of RBCs transfused in the epoetin group. Overall, to avoid 1 unit of blood transfusion, the

number of patients needed to treat was 10.[28] Further randomized clinical trials are necessary to define the optimal role of the EGFs in critically ill patients.

Other indications that are beyond the scope of this article are anemia associated with human immunodeficiency virus treatment and prophylactic EGF use in elective surgical procedures among patients who are anemic or at risk for significant blood loss from surgery. The use of an EGF in congestive heart failure and pediatric patients is being investigated.

Erythropoietic Growth Factors: Cost Assessment

Once therapeutic equivalence is established between the EGFs, a complete pharmacoeconomic analysis is necessary as part of any TI evaluation. EGF costs change according to the manufacturer, drug pricing contracts, group purchasing organization affiliation, wholesaler, and market share. Additionally, product bundling may be important in the determination of overall cost. Frequent changes in the manner and amount of reimbursement by Medicare and other insurers complicate formulary decisions. In the inpatient setting, drug acquisition cost is paramount, since each admission is only allotted a set amount of reimbursement based on the diagnosis related group. Other costs that must be considered are indirect expenses associated with administration, monitoring, and adverse effects.

From the inpatient hospital pharmacy standpoint, the choice of EGF used in the outpatient clinic setting may have a significant impact on the overall economic picture of the department, especially if operated under the same cost center. The use of one particular EGF for use in both settings will smooth the transition from outpatient to inpatient, and back again. Additionally, this will maximize market share advantage of the selected drug, for optimal pricing. The market share of a product typically determines the rebates that are available. Thus, a healthcare system that finds itself with no market share dominance is usually at the worst economic point. With reimbursement constantly diminishing, no one can afford to be "caught in the middle". It is important to recognize that in the hospital clinic, Medicare's Outpatient Prospective Payment System reimbursement changes yearly, which will impact the pharmacoeconomic analysis.

An evidence-based financial calculator has been developed to assist in managing the substantial expense associated with the EGFs and in formulary decision-making. This calculator compares the net cost of the 2 standard-of-practice regimens: epoetin 40,000 units per week and darbepoetin 100 mcg per week (given as 200 mcg Q2W in most patients).[29]

Looking only at drug cost, it would seem feasible to dose inpatients with epoetin 10,000 units 3 times weekly. This strategy would theoretically reduce inpatient cost through less use of an EGF. However, in this setting, the general hospital length of stay is not appropriate to assess the inpatient EGF of choice. Rather, the erythropoietic length of stay (ELOS) is the appropriate parameter to consider. For example, most ELOSs are 8 days or longer, which would require at least 4 doses of 10,000 units of epoetin, and would not confer an economic advantage.

Another consideration is the impact of outpatient therapy on inpatient dosing. As the evidence for extended dosing intervals accumulates and this becomes the standard of practice, the EGF that is administered less frequently may have an advantage. The use of extended interval dosing in outpatients may reduce the need for inpatient administration. The Figure (page 10) illustrates this principle: it compares the number of doses of EGF required in a 15-day period by a patient being dosed TIW (EGF1), QW (EGF2), or Q2W (EGF3). The highlighted area represents a period of hospitalization.

It is clear that from the inpatient hospital standpoint, the EGF that is dosed less frequently (Q2W) is the preferred agent, because the patient may not even require a single dose during an inpatient stay. The shorter the dosing interval, the greater the number of doses that may be required during a hospitalization.

A recent retrospective chart review demonstrated this point. Sixty-two patients with chemotherapy-induced anemia who were receiving darbepoetin as outpatients were admitted to the hospital, with a mean length of stay of 8.4 days. Ninety-two percent of the patients did not require any doses of darbepoetin during their hospitalization, which resulted in a cost savings of about $15,000 over 6 months.[30]

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Day	M 1	T 2	W 3	T 4	F 5	S 6	S 7	M 8	T 9	W 10	T 11	F 12	S 13	S 14	M 15
EGF1	X		X		X			X		X		X			X
EGF2	X							X							X
EGF3	X														X

■ Hospitalization

Figure. Comparison of EGF dosing intervals during hospitalization.

An example of a clinically and economically successful TI has been reported in the CKD population among dialysis patients. A TI was established to convert patients from one EGF to another, depending on the setting in which they were being treated. Patients stabilized on epoetin as outpatient therapy were converted to darbepoetin as inpatient therapy, then back to epoetin as outpatient therapy after discharge (E-D-E). A study of 141 of these dialysis patients found that the Hb was maintained when they were converted to darbepoetin at hospitalization. In the hospital, the majority of patients (64%) were administered darbepoetin doses less than 60 mcg. When compared with a cohort of patients who were receiving epoetin as outpatients but remained on epoetin during the inpatient stay and again at discharge (E-E-E), the E-D-E converted patients had an average cost savings of $283 per admission, for a total savings of $35,910.[21]

Pharmacy & Therapeutics Committee Evaluation and Process

The P&T Committee must critically evaluate the clinical and pharmacoeconomic data associated with a TI. When considering a TI program with the EGFs, it is necessary to comparatively evaluate the drugs in terms of efficacy, safety, US Food and Drug Administration-approved indication, and other factors, such as dosing convenience. Table 4 summarizes this information.

For the 2 major indications, cancer-associated anemia and anemia of CKD, epoetin and darbepoetin have demonstrated comparable safety and efficacy; thus, they are both indicated for these conditions. In terms of dosing convenience, darbepoetin has the advantage over

epoetin in cancer-associated anemia, because it is given less frequently and it reduces the number of times that patients have to return to the clinic. In the setting of CKD with dialysis, neither product's dosing has an impact on patient convenience, because they have to go to a dialysis clinic several times a week. Darbepoetin does have more convenient dosing in CKD nondialysis patients, who typically do not have to go to the clinic as frequently. For other indications, such as anemia associated with critically ill patients and MDS, sparse clinical data limit selection of one drug over another.

The P&T Committee would next critically review the pharmacoeconomic data, as discussed. Committee approval is required to establish and approve the policies and procedures associated with the TI on a day-to-day basis.

Table 4. EGF Comparison

	Cancer		CKD		Other*	
	Epo	Darb	Epo	Darb	Epo	Darb
Efficacy	✔	✔	✔	✔	?	?
Safety	✔	✔	✔	✔	?	?
Indication	✔	✔	✔	✔	–	–
Dosing convenience		✔	✔	✔	?	?

*Critical care, MDS
Darb=darbepoetin; Epo=epoetin

The P&T Committee must also establish exclusion criteria that allow the use of the "nonformulary" EGF in a select population, which typically include indications for which the formulary agent does not have labeling

or sufficient clinical evidence. Administrative procedures for the physician who wishes to order the nonformulary EGF must be established. Finally, the health system or institution should have a means for monitoring the safety and efficacy of the TI, as well as economic measures and the compliance rate.

Therapeutic Interchange Implementation

Once a thorough evaluation of both agents is complete, implementation of the TI program can begin, according to the following sequence:[2,4]

• **Baseline information** should be collected, including an MUE, an individualized needs assessment, and a literature search for all relevant clinical information. The MUE should identify baseline usage patterns, and should include the patient population; treatment criteria; initial EGF doses, escalation, and discontinuation; monitoring; iron stores; transfusion rates; and duplicate EGF therapy. The medical literature should be thoroughly searched for all evidence of efficacy, safety, and pharmacologic profiles, and comparative pharmacokinetic and pharmacodynamic data from clinical trials.

• An **economic assessment** is performed. This economic modeling should include an analysis of inpatient versus outpatient use; individual acquisition cost, including discounts and volume-share–based and market-share–based rebates; product bundling; payer mix; reimbursement rates; and co-pays.

• **Practice guidelines** are developed for EGF usage, through the work of a multidisciplinary committee. This includes all relevant protocols and tools, such as: a conversion chart, physician order sheets, laboratory-parameter monitoring, iron-stores monitoring with replacement therapy as needed, and documentation forms. It should also allow the prescriber some flexibility in ordering the nonformulary EGF on an individual patient basis or for specific clinical situations. Also at this stage, consideration should be given to the potential role of the information systems specialists in the TI. For example, order entry screens may be created to facilitate the TI when the physician orders the nonformulary medication, by informing the technician of the proper dosage/schedule conversion.

Specific selection criteria that define the patient population for the TI must be established. To maintain continuity of care, a system must be in place at discharge to convert patients in whom an interchange has been made back to their original EGF, at the proper dosage and schedule. Typically, this involves the creation of a discharge instruction sheet, which informs the primary care physician of the interchange and when the next dose is due.

Table 5 illustrates the guideline for converting patients from epoetin to darbepoetin, as cited in the product information.[16]

Table 5. Conversion From Epoetin to Darbepoetin

Previous Weekly Epoetin Dose (units/Week)	Weekly Darbepoetin Dose (mcg/Week)
<2500	6.25
2500 to 4999	12.5
5000 to 10,999	25
11,000 to 17,999	40
18,000 to 33,999	60
34,000 to 89,999	100
≥90,000	200

The initial dose of darbepoetin is estimated based on the weekly epoetin dose at the time of conversion. Due to the longer serum half-life, darbepoetin should be administered QW if the patient is receiving epoetin 2 to 3 times weekly or Q2W if the patient is receiving epoetin once weekly. This dose may require subsequent adjustment, based on Hb response.[16]

• **Formulary action** is the formal approval process through the P&T and other appropriate committees. Along with a thorough clinical and economic analysis, this step should include an assessment of the institution's ability to implement the TI. Tactical and administrative issues, such as program development, physician and staff education, and documentation should be addressed. From a legal standpoint, this process should determine that cost is a secondary

consideration, preceded by clinical efficacy and safety. Education is essential for successful TI implementation and use; educational programs must target prescribers, pharmacists, nurses, and any other relevant staff. Additionally, this process should ensure that a means of proper outcomes monitoring is established.

- The **TI** is initiated. An automatic therapeutic interchange upon receipt of the physician's order is most efficient in achieving conversion.

- *Program assessment* is conducted. Here, clinical outcomes and cost savings are evaluated according to predetermined criteria and time intervals. An evaluation of patient outcomes, in terms of safety and efficacy, is conducted on a regular basis to make sure they are not worsened as a result of the TI. Additionally, the impact of the interchange on the economics of the health system must be carefully analyzed and documented on a regular basis. A regular, comprehensive review of the TI program should yield any variances and opportunity for improvement.

Erythropoietic Growth Factor Interchange Opportunity

Oncology-associated anemia and anemia of CKD are common conditions that can be treated effectively with an EGF. Nationwide, the EGFs rank within the top 15 drug expenditures, and their use continues to escalate.

Epoetin and darbepoetin are: 1) pharmacologically equivalent and interchangeable; 2) equivalent in efficacy, safety, and durability; and 3) suitable for TI. Thus, the selection process of one EGF over another must involve P&T Committee process and support, including a thorough analysis of cost, operational issues such as reduced frequency of dosing, or other advantages. Once a formulary decision has been made, TI is an effective tool to maximize formulary compliance and ensure appropriate resource use. This strategy has been implemented by many health systems that use TI to manage their EGF use and cost. Following the institution of a TI program, outcomes must be measured on a regular basis to identify program compliance as well as opportunities for improvement.

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Post-test

KO is a director of pharmacy in a large health system who consistently exceeds his drug budget. An expense report shows that the blood growth factors comprise a significant portion of his top 15 drug expenditures.

1. Which one of the following interventions may help KO manage his growth factor expenses?

   a. Generic substitution

   b. Therapeutic interchange (TI)

   c. Computerized physician order entry

   d. Bar coding

2. At the next P&T Committee meeting, KO presents data for a proposed EGF TI. Which of the following criteria are required to be reviewed?

   a. Pharmacologic equivalence

   b. Clinical evidence

   c. Pharmacoeconomic analysis

   d. Policies and procedures

   e. All of the above

3. Which of the following statements about the EGFs epoetin and darbepoetin is not true?

   a. Head-to-head studies in oncology-associated anemia have demonstrated their therapeutic equivalence.

   b. Standard-of-practice dosing in oncology-associated anemia is either epoetin 40,000 units once weekly or darbepoetin 200 mcg every 2 weeks.

   c. Prolonged dosing intervals are only being studied with darbepoetin.

   d. Both epoetin and darbepoetin are indicated for the anemia of CKD, in dialysis and nondialysis patients.

4. A TI of darbepoetin for epoetin is approved and initiated. Which of the following criteria should KO review to determine if the TI program is appropriate and effective?

   a. Patient outcome, in terms of Hb levels and any adverse effects

   b. EGF expense reports

   c. Product information

   d. Inventory

   e. Both a and b