PERSPECTIVE

Oral Chelators Deferasirox and Deferiprone for Transfusional Iron Overload in Thalassemia

Major: New Data, New Questions.

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ABSTRACT

For nearly 30 years, patients with transfusional iron overload have depended on nightly
deferoxamine infusions for iron chelation. Despite dramatic gains in life expectancy in the
deferoxamine era for patients with transfusion-dependent anemias, the leading cause of death for young adults with thalassemia major and related disorders has been cardiac disease from myocardial iron deposition. Strategies to reduce cardiac disease by improving chelation regimens have been of the highest priority. These strategies have included development of novel oral iron chelators to improve compliance, improved assessment of cardiac iron status, and careful epidemiologic assessment of European outcomes with deferiprone, an oral alternative chelator available for about a decade. Each of these strategies is now bearing fruit. The novel oral chelator deferasirox was recently approved by FDA; a randomized clinical trial demonstrates that deferasirox at 20-30 mg/kg/day can maintain or improve hepatic iron in thalassemia as well as deferoxamine. A randomized trial based on cardiac T2* MRI suggests that deferiprone can unload myocardial iron faster than deferoxamine. Retrospective epidemiological data suggest dramatic reductions in cardiac events and mortality in Italian subjects exposed to deferiprone, compared to deferoxamine. These developments herald a new era for iron chelation, but many unanswered questions remain.
INTRODUCTION

In this issue of *Blood* are reports of two randomized clinical trials and a large retrospective epidemiology study, which represent crucial advances in the field of oral agents to treat transfusional iron overload in thalassemia.1-3 Here I will summarize the results of these studies, point out some of their strengths and weaknesses, and propose one hematologist’s view of where this work leaves the field.

Three Iron Chelators – parenteral vs. oral.

Deferoxamine (DFO; Desferal® and generic) has been the standard iron chelator since the 1970s. DFO is both safe and effective for transfusional hemosiderosis. A hexadentate chelator, it binds iron tightly, and the iron:DFO complex is excreted in both urine and stool. DFO is administered as long parenteral infusions, because the plasma half-life is short (minutes), and it is not active orally. Thus, it is given as an overnight subcutaneous infusion, 5-7 nights/week. The DFO:iron chelate is charged, and does not readily enter and leave cells.4 Parenteral administration and the daily nuisance of an infusion pump hinder optimal compliance. Nevertheless, in the DFO era, over the past generation, dramatic strides in survival of thalassemia patients have occurred.5

Deferiprone (Ferriprox® and others) is an orally active hydroxypyridineone, first used in humans in 1987. Deferiprone is a bidentate chelator (three molecules surround one iron ion). An advantage of this compound is that the iron(III) chelate of deferiprone carries no net charge, and therefore can penetrate membranes easily, allowing removal of potentially toxic iron from tissues.6 Many *Blood* readers are aware of a controversy over the safety of deferiprone which
arose in the late 1990s because of an observation of hepatic fibrosis during a clinical trial.\textsuperscript{7} However, in subsequent studies, this problem has not been a significant toxicity issue for Deferiprone.\textsuperscript{8} The history of deferiprone and this safety debate were well summarized in a 2003 Blood “Perspective.”\textsuperscript{9} Deferiprone often causes gastrointestinal symptoms. Idiosyncratic side effects that are potentially severe include erosive arthritis (common in patients in South Asian countries, from 5 to \(>20\%\)), and neutropenia (up to 5\% of patients), including severe agranulocytosis (up to 0.5\% of patients); close monitoring is required. Typical dosage for deferiprone is 75 mg/kg/day in three divided doses, up to 100 mg/kg daily.\textsuperscript{3,10}

Deferasirox (ICL670, Exjade\textsuperscript{®}), belongs to a new class of oral tridentate chelator, N-substituted bis-hydroxyphenyltriazoles. Deferasirox, the result of a concerted discovery program, underwent extensive safety testing and clinical trials, including preclinical studies,\textsuperscript{11} initial phase I and iron balance studies,\textsuperscript{12} phase II efficacy studies in adult\textsuperscript{13} and pediatric\textsuperscript{14} thalassemia patients, patients with a variety of anemias or unable/noncompliant with DFO,\textsuperscript{15} and the phase III clinical trial discussed here\textsuperscript{1} With a plasma half-life of 8-16 hours, once-daily dosing permits circulating drug at all times to scavenge non-transferrin-bound “labile plasma iron,”\textsuperscript{16} the chemical species responsible for tissue damage in iron-overloaded subjects, by means of toxic oxygen intermediaries.\textsuperscript{17} Deferasirox:iron complexes are excreted in the stool.

The three compounds are compared in Table 1 to properties of an ideal chelator. One “theoretical” advantage with real clinical import is access of chelators to intracellular iron, particularly in cardiac myocytes. In cultured heart muscle, Deferasirox and deferiprone have rapid access to intracellular iron pools, whereas deferoxamine does not.\textsuperscript{18} Nevertheless, high
dose continuous DFO, administered via central catheter, can dramatically reverse cardiac toxicity of iron overload.\(^4\) High-dose continuous DFO has been the ‘standard’ initial therapy for cardiac iron overload.

**Clinical assessments of chelator efficacy, and novel non-invasive measures of iron overload.**

Trials to test chelator effectiveness necessarily require a choice of a primary outcome measure. Potential “hard” endpoints or surrogates are summarized in Table 2. Different outcomes were chosen for the three studies discussed here:

(i) Hepatic iron content (HIC) by liver biopsy was used for the deferasirox vs. DFO trial. Liver biopsy has been the “gold standard” for iron balance studies, but the technique is invasive, expensive, and subject to variability within and between research subjects.

(ii) The epidemiologic study of deferiprone examines onset of symptomatic cardiac disease as the primary outcome measure. This is a compelling end point, because iron-related cardiac disease is a major clinical problem.

(iii) For their comparative trial of DFO and deferiprone, Pennell and colleagues used the cardiac MRI parameter T2* (pronounced “T-2-star”). Iron concentration in tissues (in this case the myocardium of the cardiac septum) is inversely related to T2*. Low T2* values ( <8 msec, compared to normal >20 msec) are related to risk of heart failure and death in iron-overloaded thalassemia patients.\(^{19}\) T2* reports initially raised concerns about whether it is a good surrogate for cardiac iron concentration,\(^{20}\) for technical reasons as well as the paradox that liver iron correlated poorly with cardiac T2*. These points
have been largely settled. In an iron-overload gerbil model, T2* is indeed inversely related to myocardial iron measured directly\textsuperscript{21}. The poor correlation of T2* with hepatic iron is now understood on a kinetic basis. The liver can be readily unloaded by aggressive chelation much more rapidly than can the heart, giving rise to patients with low T2* (heart still iron-loaded) while the liver has been unloaded to values previously thought of as “safe”\textsuperscript{22}.

**Randomized Clinical Trial of Deferiprone vs. Deferoxamine.**

Pennell et al\textsuperscript{3} compared oral deferiprone to subcutaneous deferoxamine in 61 thalassemia major patients without symptomatic heart failure. The entry criteria required T2* to be abnormal (less than 20 msec), but not “severe” (<8 msec), and left ventricular ejection fraction (LVEF) > 56%. Technical details of the single-breath-hold T2* method were previously published\textsuperscript{23}. SQUID (see Table 2) was used to measure HIC at baseline and 12 months. Compliance was closely monitored. The primary outcome measure was change in myocardial T2* at 6 and 12 months. The rate of rise in T2* was significantly higher to deferiprone (mean dose 92 mg/kg/day), than to deferoxamine (mean dose of 43 mg/kg, 5.7 days/wk). In addition, there was a greater increase in LV ejection fraction in the deferiprone group compared to the Deferoxamine group, all within the “normal” range. Mean HIC fell slightly in each group. Gastrointestinal symptoms and joint pain were common side effects. This prospective trial validates the prior retrospective series of Anderson et al\textsuperscript{24} which had been controversial\textsuperscript{20}. A potential weakness of the trial is the use of the surrogate T2* as primary outcome, because the clinical significance of a few more milliseconds within the mildly abnormal range is unknown if taken alone. However, taken together with *in vitro* data, and with the epidemiologic data below, this trial provides important
further evidence that despite the concerns about deferiprone chelation efficiency based on 3:1 stoichiometry, deferiprone is probably better in vivo at improving myocardial iron than deferoxamine (at the doses used).

**Efficacy of a new oral iron chelator.**

Phase III trial results for Deferasirox, in a randomized controlled comparison trial with deferoxamine, are reported by Cappellini and colleagues. The trial involved nearly 600 patients (half under age 16), with transfusion-dependent beta thalassemia. The study was designed as a non-inferiority trial, measuring hepatic iron by biopsy at baseline and after one year of therapy. Success was defined as either maintenance or improvement in HIC (depending on the baseline levels). Based on the study results, US FDA approved the drug for transfusional iron overload for patients over age 2 years in November, 2005. The drug is still under regulatory review in Europe.

This report deserves careful scrutiny from hematologists who care for patients with thalassemia and other disorders of transfusional iron overload. The dose choices for DFO and for deferasirox were based solely on baseline HIC at study entry. The decision to use this baseline value, and the choice of what are now known to be relatively low deferasirox doses, caused the study to fail to meet its overall primary endpoint (i.e., at low doses of deferasirox, 5-10 mg/kg/day, increased HIC was observed). However, at doses of 20-30 mg/kg/day, the doses for HIC >7 mg/gram dry weight, non-inferiority of deferasirox compared to DFO was established, with 60% vs. 59% achieving a successful outcome, respectively. Assessed by ferritin concentration, 20 mg/kg/day deferasirox was sufficient to maintain mean ferritin levels over 52 weeks, while 30 mg/kg
yielded a reduction in ferritin. In retrospect, several design decisions contributed to the mixed
outcome of “failure” at low doses and success at higher doses. For example, results from an
earlier phase II trial of deferasirox in children.\textsuperscript{14} which also used low doses, and which proved
ineffective, were not available in time to guide the phase III trial. As well, additional factors
proved important in deferasirox efficacy. For example, transfused iron burden was shown to be
a strong predictor of the iron response at a year.\textsuperscript{25,26} Likelihood of failing to achieve iron balance
was much higher for patients receiving more than 0.5 mg/kg/day iron.\textsuperscript{26} Adverse drug reactions
in deferasirox trials have included modest rise in creatinine, rarely clinically significant.
Increased transaminases were observed occasionally. Common side effects of deferasirox
include transient gastrointestinal symptoms in 15\%, rash in 11\%.

\textbf{An epidemiologic assessment of onset of cardiac disease in DFO or Deferiprone-treated
patients with thalassemia.}

\textit{Borgna-Pignatti and colleagues} present an interesting retrospective cohort study of cardiac
events in Italian thalassemia patients who switched from DFO to deferiprone.\textsuperscript{2} The study
included more than 500 patients with thalassemia major at 7 large Italian centers, alive in 1995,
who had neither prior heart disease nor subsequent marrow transplant. Deferiprone was given to
157 subjects during some period in the subsequent nine years, while 359 received only
deferoxamine. Many of the deferiprone patients were initially part of clinical trials, before the
drug became available on compassionate use basis in 1997, and commercially in 2000. In a time-
to-event analysis the authors noted 52 cardiac events, including 10 deaths, in patients while on
Deferoxamine, and zero events on deferiprone. The result is dramatic and unexpected, whether
one believes that deferiprone would have been given mostly to DFO-intolerant patients or not.
Although potential bias could easily arise in a retrospective study of unmatched groups, the authors have examined possible biases in a comprehensive fashion, controlling for as many as possible, and explaining the rest with admirable clarity and near-perfect patient ascertainment. This stunning finding, coupled with similar but less rigorous data from other sites, is hard to ignore. The results confirmed a smaller retrospective analysis of Piga and colleagues.27

**Cost comparison of DFO and deferasirox**

Perfect and unbiased cost comparisons among commercial versions of all three drugs are not yet possible for any single country, and national price differences abound. Although a rough first-order approximation of price ranking might be: deferiprone < deferoxamine < deferasirox, this may not be true in every country (Table 3 provides some comparisons of available costs). Non-drug obligatory costs are important as well: deferiprone therapy requires weekly CBC/differential count; deferoxamine requires ancillary supplies for infusion. Deferasirox will cost more than twice as much as DFO in the US. At least until deferasirox, chelators heretofore have not been the major cost of caring for American thalassemia patients; this dubious honor goes to the transfusions themselves.28 But the cost of deferasirox will be a significant new burden even in developed nations with strong health insurance programs, and it will be prohibitive in the developing world, without substantial discounts. An initial attempt at cost-effectiveness analysis was presented in abstract form at ASH 2005, wherein the extra cost of the medication was weighed (favorably) against the cost of illness and death from non-compliance and iron overload for DFO.29 This analysis was sponsored by the manufacturer.

**Additional recent studies of deferasirox.**
More than twenty deferasirox abstracts were presented at the 2005 American Society of Hematology meetings. These included clear evidence from both phase II and phase III clinical trials, that transfusional iron loading (expressed as mg/kg/day of transfused iron), had a dramatic effect on the ability of deferasirox doses to maintain or reduce hepatic iron\textsuperscript{25,26}, and presentation of the randomized trial of deferasirox vs DFO in sickle cell disease.\textsuperscript{30} Porter and colleagues demonstrated improved cardiac T2* with deferasirox in patients from their site in the phase II and III trials.\textsuperscript{31} Molar efficiency of DFO and deferasirox was compared by examining net iron balance as a function of input transfusional iron and chelator dose.\textsuperscript{32} These results have important implications to consider along with the phase III trial:\textsuperscript{1} chelator efficiency and clinical effectiveness \textit{in vivo} are not a function of chelate stoichiometry alone. Iron removal also depends on achievable plasma concentration, host factors, degree of loading, and rate of accessibility of stored iron to chelator.

\textbf{Clinical utility of the data from the three new studies}

How can data from these three studies best be applied to current practice? For treaters and patients, a prudent path would be first to take to heart the main messages of each of the three studies. I believe these are the take-home messages:

\textit{Cappellini et al}: At 20 - 30 mg/kg/day, deferasirox can keep most, \textit{but not all}, patients in even or negative iron balance in rough equivalence with moderate doses of Deferoxamine.

\textit{Pennell et al}: Deferiprone was able to improve not only T2* in asymptomatic patients, but these investigators also provided circumstantial evidence that their patients with “normal” LVEF had sub-clinical disease, based on improvements in LVEF with chelators. Galanello, Pennell and their colleagues have also moved ahead with a randomized, prospective, trial of
DFO+placebo vs DFO+ deferiprone in borderline T2\textsuperscript{*} status, and this study should soon be published.

*Borgna-Pignatti* et al provide the strongest evidence to date that Deferiprone should be considered cardioprotective in comparison to deferoxamine, albeit in a retrospective setting without formal matching.

But these three studies have not yet addressed some crucial questions, for example:

*What is the optimum deferasirox dose for patients with high iron intake?* Some patients with high transfusion burdens will probably have rising ferritin and HIC if treated with the approved doses of 20-30 mg/kg/day. If so, alternative strategies will be obligatory. These might include higher daily doses (which may cause more diarrhea\textsuperscript{12}), twice-daily dosing, or possible combination regimens with DFO. The latter option would offer lower average price than deferasirox alone (and ideally better net iron chelation) but would lose the advantages of oral drug. A combination of the two oral drugs, deferasirox and deferiprone, requires detailed study before it can be safely recommended.

*What is the proper role for deferiprone?* Based on side-effect profile alone, in my opinion, deferiprone is likely to remain a “second line” drug to deferasirox and deferoxamine. This is not to say that deferiprone won’t have a crucial role. In particular, Deferiprone plus DFO in some combination appears to be the emerging “treatment of choice” for significant cardiac dysfunction from iron overload, as in vivo\textsuperscript{33} and in vitro \textsuperscript{34} evidence support the biochemical rationale\textsuperscript{35}. Deferiprone is currently available only on compassionate use basis in the US. If deferasirox is
successfully used where patients used to be noncompliant with DFO, its main success will be to prevent the need for such rescue therapy altogether.

What shall we tell our patients? In our thalassemia center, we are presenting the approval of Deferasirox as a major advance and treatment option. After politely receiving this information, however, many DFO users with good compliance and HICs in safe ranges are choosing not to switch until more data become available, because they are doing fine with their pumps, and long-term deferasirox data are not yet available. We have not recommended deferasirox to patients with overt myocardial dysfunction, because no published data support this use. We now adamantly suggest deferasirox to DFO-noncompliant patients without symptomatic heart disease.

Further research is crucial. Our center is participating in an NIH-sponsored randomized trial comparing intensive DFO+deferiprone to DFO+placebo for patients with low LVEF or symptomatic heart disease, and we tell such patients that continuous infusion DFO is standard care, but addition of deferiprone on study (or for non-study participants as compassionate use) may be advantageous. Additional carefully designed studies are required to answer pressing questions about many drug combinations and treatment scenarios. Examples include both small-scale trials (e.g. pilot pharmacodynamic studies of the three drugs in various combinations), and large-scale efforts (e.g. initiation of a randomized, prospective phase III trial comparing deferasirox and deferaprone to assess relative safety, efficacy, and cardioprotection).

We look forward to a future where complications due to iron overload are rare, and our patients certainly look forward to life without “the pump.”
Acknowledgements

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## TABLE 1: Comparison of available iron chelators to an ideal chelation drug

<table>
<thead>
<tr>
<th></th>
<th>“Ideal chelator”</th>
<th>Deferoxamine</th>
<th>Deferiprone</th>
<th>Deferasirox</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route of administration</strong></td>
<td>Oral</td>
<td>Parenteral, usually subcutaneous or intravenous</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Plasma half-life</strong></td>
<td>Long enough to give constant protection from labile plasma iron</td>
<td>Short (minutes); requires constant delivery</td>
<td>Moderate (&lt; 2 hours). Requires at least three times per day dosing</td>
<td>Long, 8-16 hours; remains in plasma at 24 h</td>
</tr>
<tr>
<td><strong>Therapeutic index</strong></td>
<td>High</td>
<td>High at moderate doses in iron overloaded subjects</td>
<td>Idiosyncratic side effects are most important</td>
<td>Probably high in iron-overloaded subjects*</td>
</tr>
<tr>
<td><strong>Molar iron chelating efficiency; charge of iron (III complex)</strong></td>
<td>High, uncharged</td>
<td>High (hexadentate); charged</td>
<td>Low (bidentate); uncharged</td>
<td>Moderate (tridentate); uncharged</td>
</tr>
<tr>
<td><strong>Important side effects</strong></td>
<td>None, or only in iron-depleted subjects</td>
<td>Auditory and retinal toxicity; effects on bones and growth; potential lung toxicity, all at high doses; local skin reactions at infusion sites</td>
<td>Rare but severe agranulocytosis; mild neutropenia; common abdominal discomfort; erosive arthritis</td>
<td>Abdominal discomfort; rash or mild diarrhea upon initiation of therapy. Mild increased creatinine</td>
</tr>
<tr>
<td><strong>Ability to chelate intracellular cardiac and other tissue iron in humans</strong></td>
<td>High</td>
<td>Probably lower than deferiprone and deferasirox</td>
<td>High in clinical and in-vitro studies</td>
<td>Insufficient clinical data available; promising in laboratory studies</td>
</tr>
</tbody>
</table>

*Nephrotoxicity observed in non-iron-loaded animals has been minimal in iron-overloaded humans, but effectiveness in demonstrated only at higher end of tested doses, as discussed in text and ref 1.*
Table 2: Example of outcome measures for chelator trials, and their application for clinical practice now and in the future.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Hard outcome; compelling for studies</td>
<td>Can’t be monitored for individuals in clinical practice.</td>
<td>Cardiac disease is leading cause of death in thalassemia major</td>
<td>Remains ultimate outcome.</td>
</tr>
<tr>
<td>Cardiac Events</td>
<td>Hard outcome, compelling</td>
<td>Late event for individuals</td>
<td>Critical marker of clinical status</td>
<td>Remains crucial outcome</td>
</tr>
<tr>
<td>HIC\ by liver biopsy (both as intrinsic outcome and as surrogate for risk of cardiac disease and death[46]).</td>
<td>“Gold standard” to date. Accurately reflects total body iron status. Best assessment of fibrosis, hepatitis.</td>
<td>Invasive and uncomfortable for patients. Heterogeneous tissue iron can’t be assessed. Less reliable for iron content in fibrosis or cirrhosis.</td>
<td>Remains a critical tool, but may not be so golden considering variability and new alternatives. Imperfect surrogate for cardiac iron.</td>
<td>Use may decline if R2 MRI becomes widely available.</td>
</tr>
<tr>
<td>Cardiac iron by T2* Surrogate for risk of heart failure due to iron[19,37].</td>
<td>Non-invasive measure of cardiac iron status. T2* &lt;8 msec associated with high risk of heart disease</td>
<td>Not widely available. Not yet proven that improved T2* by chelation improves cardiac disease or death from iron</td>
<td>Very helpful for patient assessment and follow up at sites where study is available</td>
<td>Widespread use likely, if improvement correlates with improved clinical outcomes</td>
</tr>
<tr>
<td>HIC by MRI (R2 “Ferriscan” approved by FDA, other methods under study)</td>
<td>Non-invasive, potentially more accurate[38]</td>
<td>As of 2006, not widely available.</td>
<td>Ferriscan requires commercial license; few US sites signed on to date.</td>
<td>Use likely to increase if commercial hurdles are overcome</td>
</tr>
<tr>
<td>HIC by SQUID[39,40]§</td>
<td>Validated in clinical studies in comparison to liver biopsy</td>
<td>Expensive instruments, limited availability (4 in world). Not directly comparable to biopsy because of calibration variability.</td>
<td>Good alternative to biopsy for patients who live close to instruments</td>
<td>Likely to wane except for study settings if MRI methods become widespread and useful.</td>
</tr>
<tr>
<td>Serum ferritin – surrogate measure of HIC.</td>
<td>Non-invasive, inexpensive.</td>
<td>Highly variable; acute phase reactant and affected by liver disease. Single measures inadequate for assessment of current status.</td>
<td>Widely available and used. Running average over 6 months reliable for trends.</td>
<td>Likely to remain as a first-line monitoring tool between more expensive HIC assessments</td>
</tr>
</tbody>
</table>

\[Hepatic iron content; §Superconducting quantum interference device

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Table 3: Relative estimated cost of deferaprone, deferoxamine and deferasirox

<table>
<thead>
<tr>
<th>Weight</th>
<th>Deferiprone**</th>
<th>Deferoxamine: 2003 (without infusion ancillaries)</th>
<th>Deferasirox: 2006 AWP $89/gram¶</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>India cost 0.272/500 mg</td>
<td>Italy wholesale $2.04/500 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Italy wholesale $2.04/500 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate daily dose</td>
<td>25 kg child 75 mg/kg 60 kg adult 75 mg/kg</td>
<td>25 kg child 25 mg/kg 60 kg adult 25 mg/kg</td>
<td>25 kg child 20 mg/kg 60 kg adult 20 mg/kg</td>
</tr>
<tr>
<td>Annual cost</td>
<td>n/a</td>
<td>$6,760</td>
<td>$16,220</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>$6,700</td>
<td>$4,020</td>
</tr>
<tr>
<td></td>
<td>India</td>
<td>$6,760</td>
<td>$4,020</td>
</tr>
<tr>
<td></td>
<td>$350</td>
<td>$6,700</td>
<td>$4,020</td>
</tr>
<tr>
<td></td>
<td>$2,790</td>
<td>$6,700</td>
<td>$4,020</td>
</tr>
<tr>
<td>Higher daily dose</td>
<td>100 mg/kg 100 mg/kg</td>
<td>40 mg/kg 40 mg/kg</td>
<td>30 mg/kg 30 mg/kg</td>
</tr>
<tr>
<td>Annual cost</td>
<td>n/a</td>
<td>$10,810</td>
<td>$25,952</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>$10,810</td>
<td>$25,952</td>
</tr>
<tr>
<td></td>
<td>India</td>
<td>$10,810</td>
<td>$25,952</td>
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<tr>
<td></td>
<td>$470</td>
<td>n.d.</td>
<td>n.d.</td>
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<tr>
<td></td>
<td>$3,720</td>
<td>$2,680</td>
<td>$6,430</td>
</tr>
<tr>
<td></td>
<td>$1,120</td>
<td>$2,680</td>
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<tr>
<td></td>
<td>$8,940</td>
<td>$2,680</td>
<td>$6,430</td>
</tr>
</tbody>
</table>

§No published data compare contemporaneous costs in a single country. Deferasirox is available with commercial pricing in US only, while deferiprone is not available in the US.

*Generic DFO became available after the 2003 Redbook. The price now ranges from well below $14/500 mg for generic DFO to more than $20/500 mg for brand name. Neither discounts nor markups to AWP are considered for these estimate. Infusion costs (pumps, needles, tubing, diluent) vary widely among US payers and among states and countries, and could add up to a few thousand dollars annually to DFO costs.

**Deferiprone monitoring includes weekly CBC/differential count, compared to monthly CBC for the other drugs; this adds more than $1000 to the annual drug cost at US prices. Costs based on exchange rates 47 rp/$US for deferiprone, and $US1.20/Euro. Italian costs from University of Ferrara.

¶ Price information courtesy of Novartis Medical Affairs, and cited in Cost Effectiveness abstract.
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Oral chelators deferasirox and deferiprone for transfusional iron overload in thalassemia major: new data, new questions

Ellis J. Neufeld