Deferasirox: a novel, once-daily oral iron chelator

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Regular blood transfusions for the treatment of chronic anemia inevitably lead to iron overload since humans do not possess a physiological mechanism for removing excess iron. Without appropriate treatment, the cumulative effects of iron overload lead to severe organ damage and, ultimately, death. The iron chelating agent, deferoxamine, has been used effectively for over 40 years and has demonstrated the important morbidity and mortality benefits of chelation therapy. However, the demanding therapeutic regimen of frequent and slow subcutaneous infusions means that compliance can be poor, thereby compromising its effectiveness. Deferasirox (Exjade®, ICL670) is a new once-daily, oral iron chelator that has recently received approval from the US FDA, European Commission and Swiss (Swissmedic) authorities. The efficacy and safety of deferasirox has been established in a comprehensive and rigorous set of clinical studies involving adult and pediatric patients as young as 2 years of age, and in patients with a wide range of transfusion-dependent anemias. These data show the dose–dependent effects of deferasirox and have established that this new agent is as efficacious as the reference standard therapy (deferoxamine) when used at comparable therapeutic doses. The availability of this convenient, effective and well-tolerated therapy represents a significant advance in the management of transfusional hemosiderosis that allows the physician to tailor iron chelation therapy to individual patient needs.

Keywords: anemia, chelation therapy, deferasirox, deferoxamine, iron chelator, transfusional, hemosiderosis

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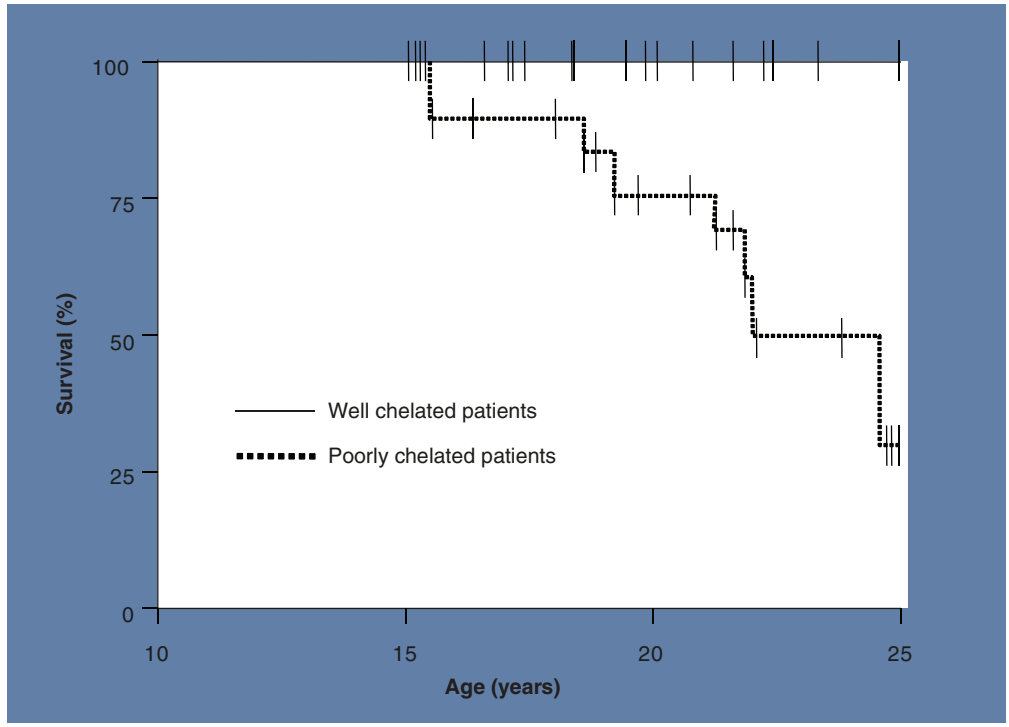
Overview of the market

In November 2005, Deferasirox (Exjade®, ICL670) a novel, once-daily oral iron chelator received approval from the US FDA and Swissmedic for the first-line treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients (aged 2 years and over). The introduction of this agent is predicted to be a significant step forward in the treatment of patients with transfusional iron overload.

Long-term blood transfusion therapy is a routine and life-giving treatment for many patients with chronic anemias, including β-thalassemia major, myelodysplastic syndromes (MDS), and sickle cell disease (SCD). The human body has many mechanisms to absorb, transfer and store essential dietary iron, but none to excrete excess amounts. As every unit of transfused blood contains 200–250 mg of iron, cumulative iron overload is therefore an inevitable consequence of chronic transfusion therapy [1]. The liver is the principal site for excess iron storage and is used as a marker of total body iron burden [2]; however iron is also deposited in other parenchymal tissues, including the heart and endocrine system. This deposition leads to ongoing damage and ultimately, organ failure [3,4]. Without treatment, the prognosis for patients with iron overload is poor [5].

Iron chelation therapy involves the use of a drug that is capable of binding iron in the body to form a chelate that can be readily excreted. Through more than 40 years of clinical use, the morbidity and mortality benefits of the current reference standard iron chelator, deferoxamine (Desferal®, DFO) have been established unequivocally. Indeed, patient survival is significantly improved in patients born after DFO became available, compared with those for whom iron chelation therapy was not an option [6–8]. Currently, DFO is the only iron chelating agent with worldwide approval for the treatment of transfusional hemosiderosis. DFO is, however, a large molecule with low oral bioavailability and a short half-life (approximately 30 min), which necessitates slow parenteral infusion over an 8–12-h period, five to seven times a week [9]. The demands of this regimen are known to have a significant impact on compliance and a large number of patients with excess iron die prematurely due to poor treatment compliance [5,10]. One study has demonstrated that the

Figure 1. Improved patient prognosis in iron overloaded β-thalassemia patients adequately chelated with DFO5.



probability of survival to at least 25 years of age in poorly chelated patients with β-thalassemia major was just a third that of patients who were well chelated with DFO (**Figure 1**) [5].

Another iron chelator, deferiprone (Ferriprox®, L1), is also currently available in a number of countries outside the USA and Canada for the second-line treatment of iron overload in a specific subset of patients – those with thalassemia major for whom DFO therapy is contraindicated or inadequate [11,12]. The use of deferiprone is limited to second-line therapy due to a lack of well-controlled efficacy data and side effects such as arthropathy (common), neutropenia and agranulocytosis (rare) [13,14]. In addition, data on its use in pediatric patients over the age of 6 years are limited and no data are available for patients less than 6 years of age. Therefore, while deferiprone is a treatment option for some patients who are unable to be adequately maintained with DFO, the need for convenient, effective and well-tolerated iron chelation therapy is apparent. Deferasirox offers a number of advantages over existing chelating agents, which are summarized in **Table 1** and discussed in this review.

Introduction to deferasirox

Deferasirox has been developed in response to an overwhelming clinical need for a convenient, effective and well-tolerated iron chelating agent. The long half-life (8–16 h) means that deferasirox need only be taken once-daily to provide 24-h chelation coverage. It is administered orally, and tablets should be completely dispersed by stirring in water, orange juice or apple juice until a fine suspension is obtained; this formulation makes it easier for pediatric patients to take. Any residue should be resuspended in a small volume of liquid and swallowed to avoid introducing variability in bioavailability. For the same reason, deferasirox should be taken on an empty stomach at least 30 min before food due to the properties of the active molecule (ICL670) [15].

The active molecule is a highly lipophilic, 99% protein-bound, N-substituted bishydroxyphenyltriazole (**Figure 2**) selected from more than 700 compounds screened as part of a rational drug development program. As it is a tridentate iron chelator, two molecules are required to form a stable complex with each iron ($Fe^{[3+]}$) atom.

Table 1. Comparison of current iron chelators.

	Deferoxamine	Deferiprone	Deferasirox (as of March 2006)
Indication	First-line treatment of iron overload	Second-line treatment of iron overload in patients with thalassemia major for whom DFO therapy is contraindicated or inadequate	First-line treatment of chronic iron overload due to transfusional hemosiderosis in patients ≥ 2 years of age
Standard dose	25–60 mg/kg/day	75 mg/kg/day	20–30 mg/kg/day
Route of administration	Subcutaneous (8–12 h, 5 days/week) or intravenous	Oral (tablets taken 3-times a day)	Oral (once-daily, dose-dispersed in water, orange juice or apple juice)
Half-life	20–30 min	3–4 h (rapidly glucuronidated and rendered ineffective)	8–16 h
Excretion	Urinary, fecal	Urinary	Fecal
Adverse effects	Local reactions, allergic ophthalmologic, auditory, growth retardation if given in excess	Gastrointestinal disturbances, agranulocytosis/ neutropenia, arthralgia and arthropathy	Gastrointestinal disturbances, rash, mild non-progressive creatinine increase, ophthalmologic, auditory
Availability	Licensed worldwide (over 40 years of clinical use)	Licensed outside USA/Canada	12 countries, including the USA and Switzerland*

**At the time of press; other applications submitted and/or approvals pending.*

Preclinical evaluation

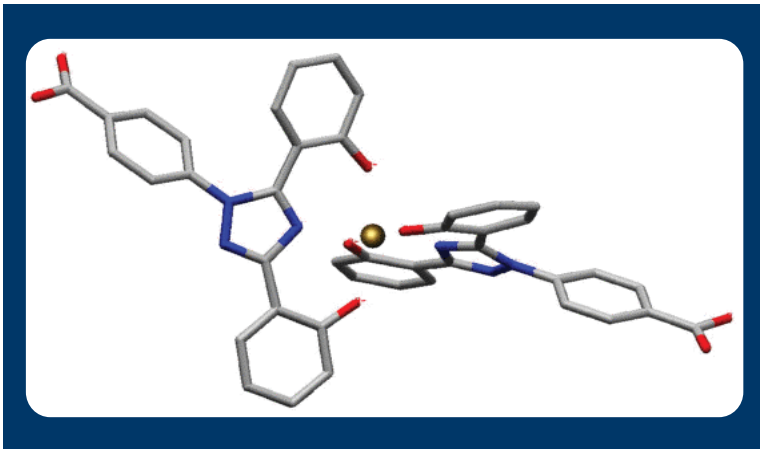
A range of animal models have demonstrated oral deferasirox to be rapidly absorbed and capable of efficiently and selectively mobilizing tissue iron and promoting its excretion [16,17]. The iron complex is sufficiently inert to be excreted in the feces, rather than being redistributed, a property that has been confirmed in the clinical evaluation of deferasirox [17–19]. In an iron overloaded rat model, the efficiency of deferasirox (defined as the ratio of iron excreted:theoretical amount of iron that can be bound by the dose given) was demonstrated to be extremely high, being 18% at doses of 50 and 100 mg/kg. In comparison, DFO (administered subcutaneously) had an efficiency of only 3–4% and deferiprone of approximately 2% [16]. The efficacy of deferasirox to reduce iron burden has been clearly demonstrated in a range of animal models, producing significant reductions in liver iron concentration (LIC) and demonstrating greater efficacy than DFO and significantly greater efficacy than deferiprone [16,17]. Iron is a physiologically important element that plays an essential role in erythropoiesis, oxygen transport, oxidative energy production, mitochondrial respiration, the inactivation of harmful oxygen radicals and DNA synthesis. The potential for deferasirox to affect the normal absorption of dietary iron has therefore been examined, and the rat model demonstrated that deferasirox does not affect normal homeostatic uptake of dietary iron [16,17].

As cardiac failure due to iron overload is a key cause of morbidity and mortality in patients with transfusional hemosiderosis, it is important to understand the effects of iron chelation therapy on cardiac iron load, and the relationship between iron levels in different organs of the body. Early evidence in cultured rat heart cells demonstrated the ability of deferasirox to remove iron directly from iron-loaded myocardial cells [20]. Additionally, a fluorescence study of chelators in living cells clearly demonstrated the ability of deferasirox to access intracellular iron, including cardiomyocytes, and chelate iron [21]. A recent study of the relative efficacy of deferasirox, deferiprone and DFO in removing iron in an iron-loaded gerbil model has shown deferasirox and deferiprone to be equally effective in removing stored cardiac iron (decreasing cardiac iron content by 20.5 and 18.6%, respectively); both chelators were significantly more effective than DFO, which did not reduce biochemically assayed cardiac iron levels [22]. This was most likely due to the mode of administration, since intravenous DFO is currently the treatment of choice for siderotic cardiac failure, having been shown to rapidly remove 'toxic' iron from the plasma [23,24]. In addition to preclinical data, preliminary clinical data show that deferasirox is effective for removing excess iron from the heart [25]. This is an interesting and exciting period for iron chelation therapy as all current iron chelators appear able to remove iron from the heart [26–28]. Studies of chelator-mediated body iron clearance are ongoing in the clinical setting.

Clinical evaluation

Deferasirox has been assessed in a comprehensive series of clinical studies involving over 1000 patients with a wide range of transfusion-dependent anemias at once-daily doses of

Figure 2. Chemical structure of deferasirox.



Deferasirox is a novel, orally active tridentate iron chelator with a high affinity and specificity for iron [16].
Note the three polar interaction sites in the binding pocket.

5–30 mg/kg (Table 2). As many patients with chronic anemia will require transfusion therapy from childhood, the deferasirox clinical evaluation program has also focussed on pediatric patients, including those as young as 2 years of age, to investigate the efficacy and safety of deferasirox in this important population.

Pharmacokinetic properties of deferasirox

The first clinical study of deferasirox (Study 101) demonstrated that the serum concentration of deferasirox is proportional to dose (Figure 3) [18]. Unbound deferasirox had a mean half-life of 11–19 h (Table 3), supporting the once-daily dosing regimen used throughout the clinical trial program.

The pharmacokinetic profile of deferasirox in pediatric patients with β-thalassemia major has also been evaluated after administration of single and multiple oral doses (Study 106). The results showed no differences between children (aged < 12 years) and adolescents (aged ≥ 12 years) in terms of C_{max}, AUC and half-life, although exposure to deferasirox was approximately 20–30% lower than that observed in adult β-thalassemia patients in previous studies [29].

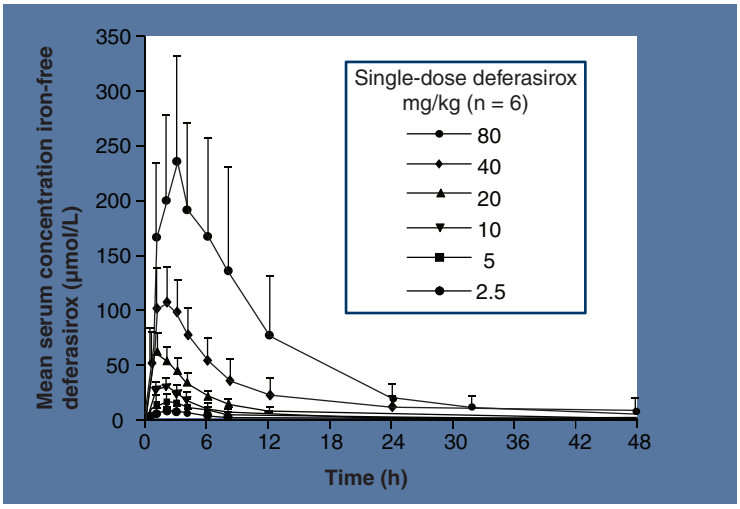
The long half-life of deferasirox is important as it has been established that chelation coverage with other available iron chelators is limited to periods of drug exposure, leaving the body exposed to levels of labile plasma iron (LPI), a component of non-transferrin-bound iron, which is considered to contribute to the toxicity of iron overload. In patients treated with DFO or deferiprone, LPI levels fluctuate over a 24-h

Table 2. Summary of deferasirox clinical evaluation program.

Study (Phase)	Primary end point	Population	Design	No. of patients
101 (Phase I)	Safety and tolerability	Thalassemia (adults)	Single-dose defining	24
104 (Phase I)	Iron balance	Thalassemia (adults)	Multiple dose	24
105 (Phase II)	Safety	Thalassemia (adults)	Randomized deferasirox 10 or 20 mg/kg/day versus DFO	71
106 (Phase II)	Safety	Thalassemia (pediatric)	Single arm, deferasirox 10 mg/kg/day	40
107 (Phase III)	LIC	Thalassemia (adult and pediatric)	Randomized deferasirox 5–30 mg/kg/day vs DFO 20–60 mg/kg/day	586
108 (Phase II)	LIC	Adult and pediatric patients with a range of transfusion-dependent anemias (thalassemia, myelodysplastic syndrome, Diamond–Blackfan and other rare anemias)	Single arm, deferasirox 5–30 mg/kg/day	Thalassemia (85); other (99)
109 (Phase II)	Safety	Sickle cell disease (adult and pediatric patients)	Randomized deferasirox 10–30 mg/kg/day vs DFO 20–60 mg/kg/day	195

DFO: Deferoxamine; LIC: Liver iron concentration.

Figure 3. Mean plasma concentrations (+ SD) of deferasirox following single-dose administration [18].



period and are at times poorly controlled as levels significantly rebound between doses [30]. As deferasirox is present in the circulation and provides chelation coverage over the entire 24-h period, it may provide greater control of LPI and this is being investigated as part of the deferasirox clinical trial program.

Clinical efficacy

An initial dose-escalation study conducted in patients with β-thalassemia and transfusional iron overload (Study 104) demonstrated efficacy and a chelation efficiency of up to 20.5% [19]. Data from the 1-year, Phase II comparative study of transfusion-dependent thalassemic patients (Study 105) provided the first evidence that deferasirox was comparable to the current reference standard, DFO. In this study, a single daily dose of deferasirox 20 mg/kg/day was as effective as DFO 40 mg/kg/day in the removal of iron from body stores. A subsequent large-scale, Phase III trial (Study 107) has confirmed these findings in a population of 586 adult and pediatric patients (aged as young as 2 years) with transfusion-dependent β-thalassemia [31]. Chelator dose was assigned according to baseline LIC; those with baseline LIC below 7 mg Fe/g dry weight received deferasirox 5 or 10 mg/kg/day or DFO less than 25–35 mg/kg, and those with baseline LIC of 7 mg Fe/g dry weight or higher received deferasirox 20 or 30 mg/kg/day or DFO from 35 to greater than or equal to 50 mg/kg.

This study confirmed the dose-related efficacy of deferasirox and demonstrated that patients with baseline LIC values of 7 mg Fe/g dry weight or more, who were treated with deferasirox doses of 20 and 30 mg/kg/day or DFO doses of 35 or greater than (or equal to) 50 mg/kg, had similar reductions in LIC, changes in serum ferritin, and net body iron balance in both treatment groups (**Figure 4**). However, the nature of the protocol design resulted in patients with LIC values below 7 mg Fe/g dry weight receiving lower doses of deferasirox relative to DFO than patients with a LIC of 7 mg Fe/g dry weight or more. This was because patients who were receiving DFO therapy at study entry were allowed to continue on their current dose even if it was higher than would have been allocated. The net result was that in the lower deferasirox dose ranges, doses were not comparable (ratio 1:4, deferasirox vs DFO; stoichiometric equivalence ratio 1:2). Equivalent maintenance or reduction of LIC was therefore not seen in the overall population, but it was clearly evident that at deferasirox doses of 20 mg/kg/day (which is the recommended starting dose in many patients) iron balance was achieved, and at doses of 30 mg/kg/day significant reduction in iron burden was observed [31]. In addition to the pediatric data obtained in Study 107 (n = 292), preliminary data from Study 106 support the value of deferasirox in this patient group [32].

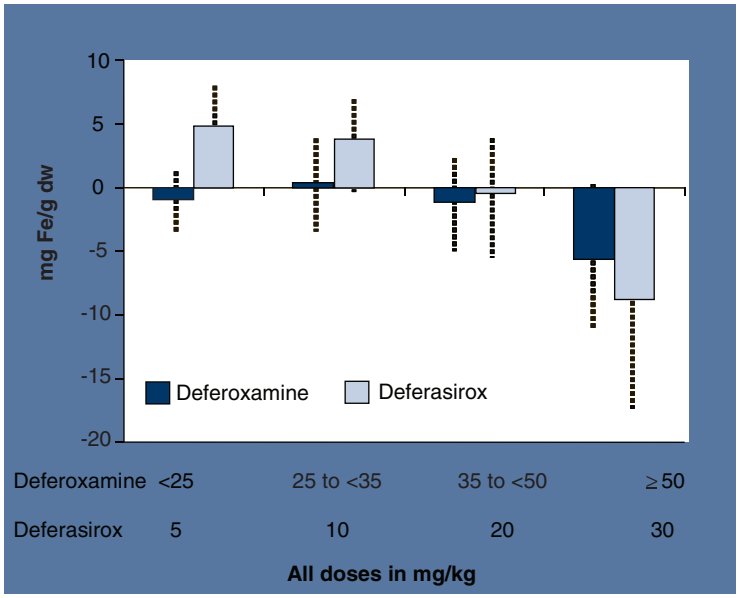
While the majority of the clinical evaluation of deferasirox has focused on patients with thalassemia (which serves as the model of transfusional hemosiderosis), clinical trials have also included patients with a range of chronic anemias including MDS, SCD, Diamond–Blackfan and other rare anemias. As the pathogenesis of

Table 3. Pharmacokinetic parameters of deferasirox following single oral administration.

Dose (mg/kg/day)	C_{max} (µmol/L)	$AUC_{0–24}$ (h.µmol/L)	Half-life (h)
2.5	9.4 ± 3.7	70 ± 20	12 ± 9
5	19.3 ± 5.2	140 ± 50	11 ± 5
10	32.3 ± 6. 9	200 ± 50	14 ± 11
20	64.3 ± 17.2	390 ± 70	18 ± 7
40	119.4 ± 27.4	890 ± 330	19 ± 6
80	240.7 ± 96.4	2360 ± 1180	18 ± 8

Adapted from [18].

Figure 4. Deferasirox produces a reduction in the absolute LIC dependent on the dose administered (mean ± SD).



In this heavily transfused population, doses of 5 and 10 mg/kg were too low to maintain or reduce absolute liver iron concentration (LIC), whereas a dose of 20 mg/kg maintained LIC, and 30 mg/kg reduced LIC (Results from Phase III, Study 107) [31].

chronic iron overload is likely to be similar in patients with different underlying conditions, it is likely that the efficacy results will be comparable. Data are beginning to accumulate in other patient types and preliminary data from patients with MDS involved in Study 108 have been presented. These demonstrate significant, dose–dependent decreases in LIC over the 1-year treatment period, which were mirrored by dose–dependent effects on serum ferritin levels and were similar to results observed in thalassemia patients [33].

Tolerability

Thorough clinical evaluation of deferasirox in adults and children with different chronic anemias has shown deferasirox to be generally well tolerated, with no evidence of the serious adverse events associated with other chelators such as agranulocytosis, neutropenia or arthropathy [31–33]. The most frequent reactions reported during chronic treatment include transient, mild-to-moderate gastrointestinal disturbances, mild, non-progressive rises in serum creatinine (generally within upper limit of normal) and transient mild-to-moderate skin rash. These events rarely required drug discontinuation and many resolved spontaneously. There were no cases of moderate to severe renal insufficiency or renal failure and no patients permanently discontinued therapy due to creatinine increases. Studies to date indicate that these mild, non-progressive increases in serum creatinine are temporary and reversible; extension studies are ongoing to collect long-term data. Two patients (2/703; 0.3%) experienced elevations in alanine aminotransferase more than five-times the upper limit of normal, reflecting an adverse effect on the liver, for which an association with deferasirox treatment could not be ruled out. Deferasirox is also generally well tolerated in children as young as 2 years of age, with a safety profile similar to that observed in adults [32]. To date, sexual and physical development have proceeded normally during treatment with deferasirox [34]; longer-term studies are ongoing to confirm this finding.

The metabolism and elimination of deferasirox and the iron chelate (Fe–[deferasirox]$_2$) is primarily by glucuronidation followed by hepatobiliary excretion into the feces. No significant drug–drug interactions have been identified to date.

Expert commentary

While DFO has proven to be an essential, life-saving element of the management of chronically-transfused patients, it is well known that compliance with the demanding therapeutic regimen significantly limits the ability to adequately control body iron levels. It can therefore be anticipated that a convenient, effective and well-tolerated oral iron chelator is a significant development in this therapeutic area with the potential to improve compliance and therefore achieve optimal benefits in terms of morbidity and mortality. With increasing awareness of the value of transfusion therapy in a range of chronic anemias, and the recent recommendation to establish routine transfusion therapy in very young SCD patients at risk of stroke [35], the application of this approach is likely to become increasingly widespread. Deferasirox is likely to facilitate these changes in clinical practice, potentially increasing the number of patients for whom beneficial transfusion therapy is considered. This new agent may also allow treatment to be initiated at an earlier stage in the disease course than at present due to the excellent efficacy and tolerability profile combined with the advantages of once-daily oral administration.

Highlights

- Iron overload is an inevitable consequence of regular transfusion therapy.
- Effective iron chelation therapy significantly reduces the morbidity and mortality of patients with transfusional hemosiderosis, but compliance with daily therapy is crucial.
- Deferasirox is a once-daily oral iron chelator that has been rigorously evaluated in a worldwide clinical trial program involving more than 1000 patients with a diverse range of transfusion-dependent anemias, including 292 pediatric and adolescent patients.
- Deferasirox has been shown to be effective in reducing body iron levels, producing statistically significant and clinically relevant reductions in LIC and serum ferritin.
- With optimal dosing, the efficacy of deferasirox is comparable to that of the current reference standard therapy, deferoxamine.
- Pharmacokinetic evaluation of deferasirox shows 24-h chelation coverage is well tolerated across the range of underlying anemias in patients 2 years of age and older.
- The availability of a convenient, effective and well-tolerated oral chelator will relieve patients from the burden of current therapy and could increase the number for whom beneficial transfusion is considered.

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