

## **Exjade (ICL 670, deferasirox)**

### **Advisory Committee Summary**

#### **Introduction and Background**

Exjade® (deferasirox) is proposed for use as an orally administered iron chelating agent. Chemically, Exjade is 4-(3,5-bis-(2-hydroxy-phenyl)-1,2,4 triazol-1-yl)-benzoic acid and has a molecular weight of 373.4. Two molecules of Exjade bind a single atom of iron from the soluble iron pool in the plasma. Subsequently, this complex is excreted, primarily in the stool. The applicant proposes that Exjade be approved for treatment of chronic iron overload in patients (aged two years and older) with congenital and acquired anemias who have developed excessive total body iron stores (hemosiderosis) due to chronic transfusion therapy.

Iron balance in the adult is maintained by equilibrium between the absorption of orally ingested iron (5-15 mg per day ingested, of which approximately 1 mg per day is absorbed) and the loss of iron that occurs when iron-containing cells (skin, GI mucosa, etc.) are sloughed from the body. The proportion of ingested iron that is absorbed is increased in persons who are iron deficient and in patients with various anemias. The normal daily loss is approximately 1 mg (menstrual blood loss and pregnancy increase this amount in women). There is no physiological mechanism for excretion of excess elemental iron from the body. Total body iron is approximately 50 mg/kg in adult men and 35 mg/kg in menstruating women (2.5-5 g). Full-term infants begin life with a body iron content of approximately 75 mg/kg, but these stores are rapidly used for the production of red cells required as body size increases.

Since iron is carefully conserved by the body, any additional iron loading adds to body iron stores. The accumulation of iron to excess in the human body is associated with significant morbidity and early mortality, although the exact mechanism by which excess iron causes tissue damage is not known. The amount of excess iron that needs to be present to produce morbidity is variable and depends on individual response and the target organ. Although any organ in the body may be affected, organ dysfunction is primarily seen in the liver, heart, pancreas, joints and endocrine organs. Most of the morbidity and mortality seen in iron overload is the result of effects on the heart.

Patients with chronic anemias often require chronic transfusion therapy. Chronic transfusion therapy is the standard of care for patients with  $\beta$ -thalassemia major because it prevents much of the developmental retardation and excess cardiac work associated with the anemia. In sickle cell anemia, patients initiate chronic transfusion therapy following the occurrence of certain events, particularly cerebrovascular accidents, to minimize the chance of recurrence. Monthly transfusional requirements of 2-3 units of

packed red cells are typical. There is approximately 1 mg of iron in each mL of transfused red cells or approximately 200 mg of iron in each unit of packed red cell transfusion. Each year of transfusions may add 5-8 gm of iron to total body stores of a patient. In these patients, the onset of organ dysfunction is variable and not necessarily related to the degree of iron overload. Subclinical cardiac abnormalities with diminished left ventricular contractility may occur when total body iron reaches as little as 20 g.

Currently, the only available therapy for transfusional hemosiderosis is parenteral Deferoxamine (Desferal®, DFO). Deferoxamine, although effective in reducing iron stores in the body, has the drawbacks of a short pharmacological half life and the need for parenteral administration. These features necessitate long term (10-12 hour) subcutaneous or intravenous (via catheter) infusions by pump daily for 5-7 days a week. However, problems with compliance with the DFO treatment regimen limit DFO use, particularly in the adolescent population.

Several studies in chronically transfused patients with  $\beta$ -thalassemia suggest that chelation of excess iron using DFO reduces morbidity and increases longevity, particularly when patients are compliant with therapy and maintain a serum ferritin below 2500  $\mu\text{g/L}$ .

The applicant's preclinical and clinical program was intended to demonstrate the efficacy and safety of the use of Exjade to lessen the effects of iron overload in patients with  $\beta$ -thalassemia. The applicant has also studied the efficacy and safety of the use of Exjade in patients with other chronic anemias requiring transfusion therapy

### **Brief Overview of the Preclinical Program**

The preclinical program included studies designed to evaluate the pharmacological and toxicological characteristics of Exjade. The results can be outlined as follows:

- Exjade is capable of inducing iron excretion in iron overloaded animals in amounts that may be clinically relevant. Liver iron concentration falls by a significant amount in these animals. Iron excretion occurs primarily through the fecal route.
- Oral and intravenous administration of Exjade in subacute and chronic animal toxicity studies indicated that the target organs for toxicity include the kidney, eye, heart, gastrointestinal tract and the biliary system.
- Juvenile animals appear to be more sensitive to the toxicity of Exjade than are adult animals. Depression of the immune system is seen only in juvenile animals.
- Although Exjade showed evidence of genotoxicity in two micronucleus tests, it was not genotoxic in any other tests performed.
- Exjade did not demonstrate carcinogenic potential in animals.

- Exjade did not demonstrate a teratogenic potential in animals.
- Fertility and reproductive performance were not altered in animals treated with Exjade.
- Exjade was shown to cross the placenta and was excreted in breast milk.

### **Brief Overview of the Clinical Program**

The applicant seeks to have Exjade approved for the following indication: “The treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis). Exjade is indicated for both adult and pediatric patients aged two years of age and over”.

In support of the indication, the applicant has performed and submitted one multicenter, randomized, active-controlled (DFO) Phase 3 trial in adult and pediatric patients with  $\beta$ -thalassemia. In addition, the applicant has submitted the results of three Phase 2 studies in patients with  $\beta$ -thalassemia, as well as interim safety results from a study of the use of Exjade in the treatment of chronic iron overload in adults and children with sickle cell anemia and its variants.

The number of patients enrolled in the four primary trials was 835, of whom 518 received Exjade and 317 received DFO. In the interim report of the ongoing study in sickle cell anemias, an additional 195 patients were enrolled, of whom 132 received Exjade and 63 received DFO. In these trials, the length of the administration of Exjade was 48 weeks, although a small number of patients received Exjade for less than 48 weeks because of adverse events, withdrawal from the study or dropout. The applicant has also submitted the results of an extension study in which 51 patients who had already received Exjade in a clinical study continued Exjade’s use for periods up to a total of 3 years. For the 650 patients who received Exjade in these studies, the mean duration of treatment was 51.8 weeks and the range of treatment was 0.1-152 weeks. Additional patients received either single or multiple doses of Exjade during Phase 1 trials and for various biopharmaceutical studies.

### **Efficacy**

The major efficacy trials are as follows:

- Study 0107 (Phase 3, Pivotal). A randomized, open-label, multicenter trial that compared the efficacy and safety of the use of Exjade to that of DFO in the treatment of chronically transfused patients with  $\beta$ -thalassemia who had hemosiderosis.

- Study 0105 (Phase 2). A randomized, open-label trial that compared the safety, tolerability and effect on liver iron concentration of the use of Exjade to that of DFO in the treatment of chronically transfused patients with  $\beta$ -thalassemia who had hemosiderosis.
- Study 0106 (Phase 2). A non-randomized study to evaluate the PK profile, safety, tolerability and effect on liver iron concentration of Exjade in chronically transfused pediatric patients with  $\beta$ -thalassemia who had hemosiderosis.
- Study 0108 (Phase 2). A multicenter, open-label, single arm, non-comparative study of the efficacy and safety of Exjade in patients who were receiving transfusions as a result of other chronic anemias and had developed hemosiderosis and in patients with  $\beta$ -thalassemia who had developed hemosiderosis and were unable to be treated with DFO.

The only adequate and well-controlled randomized Phase 3 trial was Study 0107. The other trials were either exploratory or uncontrolled. For randomized trials, blinding was not performed because it was proposed that the subcutaneous administration of placebo for 48 weeks to patients randomized to Exjade was unacceptable.

Study 0107 was a multicenter, randomized, open-label, active-controlled, parallel group, non-inferiority design trial in 586 patients with  $\beta$ -thalassemia who had transfusional hemosiderosis. The study compared Exjade to DFO, with doses of Exjade used ranging from 5-30 mg/kg/d (depending on screening LIC) and DFO doses ranging from 20-50 mg/kg/d (depending on screening LIC and/or on the patient's previous DFO dose; almost all of the patients enrolled in the trial had been receiving DFO).

The determination of LIC in each patient was accomplished by the use of one or both of two methods. The major method was by assay of a liver biopsy (standard method). The other method used a superconducting quantum interference device (SQUID) for the measurement of LIC (alternate method). In early meetings with the applicant, and in multiple communications with the applicant, the Division had questioned the validity of the use of SQUID for the measurement of LIC and stressed the need for validation of this method if it was to be used in establishing the efficacy or bioactivity of the drug. The applicant submitted documentation of validation late in the clinical program development. The documentation was reviewed by the FDA Center for Devices and Radiological Health and was found to be inadequate because magnetic signals that originated from sources (spleen, heart, blood, etc.) other than LIC had been ignored, because the sonographic location of the liver was determined while the patient was breathing normally while the SQUID measurement was made during exhalation, because the ellipsoid model of the liver and the cylindrical model of the thorax were not accurate, because iron has more than one oxidation state, and because bias may have been introduced into the results since the raw data recorded by the SQUID were first inspected by the device operators before being accepted for entry into the database. Subsequently, the applicant analyzed the correlation between liver biopsy and SQUID results in a subset

of patients and determined that SQUID underestimated LIC by a factor of 2 compared to LIC as measured by liver biopsy. In addition, it was determined that LIC measured by

SQUID varied substantially among the three institutions at which the studies were being performed.

In Study 0107, 16.3% of patients had LIC measured by SQUID alone. After the data from Study 0107 had been locked and analyzed, the applicant asked the review Division to exclude from the analysis of efficacy those patients whose LIC had been assessed by SQUID. The rationale for this request was that since the initial Exjade dose was based on LIC and since SQUID measurement of LIC apparently seriously underestimated the LIC measured by biopsy, patients dosed on the basis of the SQUID-determined LIC apparently had been under dosed. In addition, the protocol had allowed patients in the DFO arm to remain on the same dose of DFO that they had been receiving prior to enrollment (virtually all patients enrolled in the trial had already been receiving DFO) regardless of the LIC measurement. The applicant believes that this led to a disproportionately greater number of patients receiving low-dose Exjade as compared to the number receiving low-dose DFO. Of note, dose-finding results in earlier trials suggested that low doses of Exjade (i.e.,  $\leq 10$  mg/kg/d) were ineffective in inducing iron excretion sufficient to lower LIC in patients who continued to require transfusion therapy; the design of Study 0107 did not take these findings into account.

The primary analysis for efficacy for Study 0107 was based on the success rate which was calculated using LIC at baseline and after one year. Success included either the maintenance of LIC within a given range if the LIC was  $< 7$  mg Fe/g dw or a reduction of LIC if the LIC was  $\geq 7$  mg Fe/g dw. The definition of success (and failure) is shown in the table below.

**Table 6-1 Primary efficacy endpoint: success criteria (based on LIC)**

LIC at baseline	Success, if LIC after 1 year	Failure, if LIC after 1 year
$2 - < 7$ mg Fe/g dw	$1 - < 7$ mg Fe/g dw	$< 1$ mg Fe/g dw or $\geq 7$ mg Fe/g dw
$\geq 7 - < 10$ mg Fe/g dw	$1 - < 7$ mg Fe/g dw	$< 1$ mg Fe/g dw or $\geq 7$ mg Fe/g dw
$\geq 10$ mg Fe/g dw	Decrease in LIC $\geq 3$ mg Fe/g dw	Decrease in LIC $< 3$ mg Fe/g dw

Non-inferiority of Exjade compared to DFO was to be claimed if the 2-sided 95% confidence interval (CI) of the difference in the proportion of success was greater than -0.15. The applicant's primary efficacy results for Study 0107, as defined in the table above, are shown in the following table.

**Table 9-1 Success rates based on change in LIC (PP-1 population)**

	ICL670 5 mg/kg N=15	ICL670 10 mg/kg N=70	ICL670 20 mg/kg N=79	ICL670 30 mg/kg N=112	ICL670 All pts N=276	DFO All pts N=277
<b>Biopsy &amp; SQUID</b>	N=15	n=70	n=79	n=112	n=276	n=277
Success rate (n (%))	6 (40.0)	28 (40.0)	29 (36.7)	83 (74.1)	146 (52.9)	184 (66.4)
95% CI	[16.3, 67.7]	[28.5, 51.5]	[26.1, 47.3]	[66.0, 82.2]	[47.0, 58.8]	[60.9, 72.0]
Difference and 95% CI						-13.5 [-21.6, -5.4]

The results indicate that the applicant failed to demonstrate the non-inferiority of Exjade compared to DFO since the lower bound of the CI for the point estimate was -21.6 and this exceeded the pre-specified delta margin of -0.15. On reviewing the data, the applicant believed that the basis of failure was that patients were disproportionately assigned to Exjade at doses of 5-10 mg/kg/d because of SQUID-determined LIC determinations that underestimated the true LIC. Patients in the DFO arm with SQUID-determined LIC continued on the same doses of DFO that they had been receiving prior to entry into the trial rather than being required to take the dose that they would have been given if the protocol dosing had been followed.

In a post-hoc analysis of success in the subsets of patients whose LIC, measured by either biopsy or SQUID, was <7 mg Fe/g dw and ≥7 mg Fe/g dw, the applicant concluded that Exjade was non-inferior to DFO in the latter but not in the former.

**Table 9-1 Success rates based on change in LIC (PP-1 population)**

	ICL670 5 mg/kg N=15	ICL670 10 mg/kg N=70	ICL670 20 mg/kg N=79	ICL670 30 mg/kg N=112	ICL670 All pts N=276	DFO All pts N=277
<b>LIC &lt; 7 mg Fe/g dw</b>	N=15	n=70			n=85	n=87
Success rate (n (%))	6 (40.0)	28 (40.0)			34 (40.0)	72 (82.8)
95% CI	[16.3, 67.7]	[28.5, 51.5]			[29.6, 50.4]	[74.8, 90.7]
Difference [95% CI]						-42.8 [-55.9, -29.7]
<b>LIC ≥ 7 mg Fe/g dw</b>			n=79	n=112	n=191	n=190
Success rate (n (%))			29 (36.7)	83 (74.1)	112 (58.6)	112 (58.9)
95% CI			[26.1, 47.3]	[66.0, 82.2]	[51.7, 65.6]	[52.0, 65.9]
Difference [95% CI]						-0.3 [-10.2, 9.6]

One of the prespecified secondary endpoints in Study 0107 was the reduction in LIC in patients with a baseline LIC of ≥7 mg Fe/g dw. Analysis of this endpoint showed that both reduced LIC and there was no difference in the degree of reduction of LIC after 48 weeks of treatment between patients treated with Exjade compared to those treated with DFO as shown in the following table.

**Table 9-3 Change in LIC in patients with LIC greater or equal to 7 mg Fe/g dw at baseline (PP-2 population)**

Statistics	ICL670 N=185	DFO N=186	Difference (ICL670-DFO) adjusted on baseline
<b>Biopsy &amp; SQUID</b>			
n	185	186	
Mean ± SD	-5.3 ± 8.04	-4.3 ± 5.83	-0.56 ± 0.623
95% CI			[-1.79, 0.66]
p-value	p<0.001 (S)*		p=0.367 (NS)**

\* t-test for one sample (one sided): if p<0.025, significant difference (S) of the change from baseline in the ICL670 group.

\*\* Covariance analysis with baseline as covariate: if p<0.05, significant difference (S) in changes between the 2 groups at end of study.

Changes in serum ferritin levels over the 48 week length of the trial showed that, although there were large standard deviations around the mean, the serum ferritin did tend to be correlated with changes in the biopsy measured LIC. Reduction in serum ferritin and LIC was most marked in patients whose baseline LIC was >14 mg Fe/g dw as shown in the following table.

**Table 9-4 LIC and serum ferritin in patients with biopsy (PP-2 and Safety population)**

		ICL670			DFO		
		Baseline	EOS	Change	Baseline	EOS	Change
<b>LIC ≤ 3</b>	LIC	2.5 ± 0.21	10.4 ± 1.75	7.8 ± 1.9	2.7 ± 0.28	3.1 ± 1.12	0.4 ± 1.26
	Ferritin	1370 ± 904	2525 ± 1107	1155 ± 339	1366 ± 660	1476 ± 756	167 ± 501
<b>LIC &gt;3-7</b>	LIC	4.9 ± 1.08	10.1 ± 4.21	5.1 ± 3.93	5.2 ± 1.22	5.6 ± 2.63	0.4 ± 2.76
	Ferritin	1707 ± 771	2560 ± 1208	864 ± 857	1523 ± 701	1512 ± 832	-21 ± 447
<b>LIC &gt;7-14</b>	LIC	10.6 ± 2.08	10.5 ± 4.72	-0.1 ± 4.86	10.6 ± 2.03	8.8 ± 2.99	-1.8 ± 2.96
	Ferritin	2136 ± 1049	2108 ± 1095	-42 ± 673	2124 ± 874	1824 ± 892	-316 ± 573
<b>LIC &gt;14</b>	LIC	24.2 ± 7.82	15.3 ± 9.38	-8.9 ± 8.07	23.9 ± 8.06	17.0 ± 8.66	-6.5 ± 6.95
	Ferritin	3769 ± 2379	2858 ± 2092	-926 ± 1416	3627 ± 2451	2544 ± 1911	-1001 ± 1435

Study 0105 was an exploratory dose-finding study designed to evaluate the tolerability and safety of the use of Exjade compared to DFO in 71 β-thalassemia patients with transfusional hemosiderosis receiving chronic transfusion therapy. Evaluation of efficacy was a secondary objective. Patients were randomized to Exjade at a dose of 10 mg/kg/d, Exjade at a dose of 20 mg/kg/d or to DFO at a dose of 40 mg/kg/d for 5 days each week. The trial was originally 12 weeks in duration but was subsequently lengthened to 48 weeks. Assessment of LIC was performed by SQUID alone. Efficacy evaluation suggested that the original doses of Exjade used were insufficient to maintain or lower LIC at 12 weeks compared to DFO, but that increasing the dose of Exjade lowered the LIC to a degree similar to DFO at the end of 48 weeks.

Study 0106 was an exploratory, non-comparative study to evaluate the tolerability, safety and pharmacokinetics of the use of Exjade over 48 weeks in 40 pediatric β-thalassemia

patients with transfusional hemosiderosis receiving chronic transfusion therapy. All patients were begun on Exjade at a dose of 10 mg/kg/d. Assessment of LIC was performed by SQUID alone. Efficacy evaluation suggested that Exjade at a dose of 10 mg/kg/d was insufficient to prevent a rise in LIC in this patient population.

In Study 0108, 85 patients with  $\beta$ -thalassemia intolerant or non-responsive to DFO and 99 patients with other transfusion dependent anemias were treated Exjade at doses of 5-30 mg/kg/d for 48 weeks. The initial dose was determined by LIC, measured by either liver biopsy (120 patients) or by SQUID (64 patients). Dose adjustment was permitted based on measures of efficacy and safety. The success rate (as defined in table 6.1 above) for all patients was 50.5% (95% CI, 43.3, 57.8) and this did not reach prespecified statistical significance. Again, however, in the subgroup of patients with  $\beta$ -thalassemia and an LIC  $\geq 7$  mg Fe/g dw, the success rate was 61.4% (CI, 50.0, 72.8) which did meet the prespecified success rate. Similarly, there was a statistically significant reduction in

LIC ( $-6.1 \pm 8.03$ ) in this same subgroup of patients. These data are supportive of the data from the similar subgroup analysis in Study 0107.

Due to the limited numbers of patients in the submitted studies requiring transfusions for conditions other than  $\beta$ -thalassemia, there are limited data and possibly greater safety concerns in patients treated with Exjade who had other causes for transfusion-related hemosiderosis (e.g., myelodysplastic syndrome, refractory anemias, Blackfan-Diamond syndrome, etc).

A change in LIC associated with the use of Exjade was accepted by the Division as a correct measure of efficacy because it is the most well accepted clinical measure of the efficacy of an iron chelator. Nonetheless, because the most common cause of morbidity and death in iron overloaded  $\beta$ -thalassemia patients is cardiac in nature, it remains uncertain as to whether Exjade will reduce the incidence of these important clinical outcomes.

## **Safety**

The efficacy of Exjade must be viewed in relation to a number of safety concerns that have been raised during the conduct of both the preclinical and clinical studies, as well as the prospect that Exjade will be used for the lifetime of the patient.

While the size of the database is modest and the experience is restricted mostly to patients with  $\beta$ -thalassemia, the duration of therapy for most of the patients has been nearly one year, and a few patients have received Exjade for as long as three years.

In the  $\beta$ -thalassemia population, there was one unexplained sudden death in a three-year-old child who had received Exjade at a dose of 31.2 mg/kg/d for 84 days. Five patients with other chronic anemias receiving Exjade died. Three (myelodysplasia, 2, Blackfan-

Diamond syndrome, 1) were related to sepsis in the setting of neutropenia that had been present at baseline or had developed in association with the use of chemotherapeutic drugs. One patient with myelodysplasia died of recurrent thromboembolism and one of cardiopulmonary arrest. The deaths in the patients with other chronic anemias occurred from Day 27-376 after initiation of therapy. Doses in these patients varied.

Serious adverse events believed related to the drug occurred in 17 (2.6%) of patients receiving Exjade. These included four skin rashes, four gastrointestinal events and three increases in transaminases. Five patients discontinued Exjade because of serious adverse events.

Adverse events leading to drug discontinuation occurred in 17 (2.6%) of patients receiving Exjade. Most often, these included gastrointestinal disorders, skin rash, an increase in transaminases, renal abnormalities, cataract development and hyperactivity.

Adjustment in dose or temporary interruption was common, occurring in 25-53% of patients treated with Exjade. Causes for dose changes were mostly related to common adverse events, and included gastrointestinal symptoms (nausea, diarrhea, vomiting, abdominal pain), headache, rash and an increase in serum creatinine.

Laboratory safety data indicated that about 33% of patients sustained an increase in serum creatinine, albeit often with creatinine concentrations remaining within the normal range. Reduction in dose or interruption of Exjade therapy was usually associated with a fall in serum creatinine to baseline. Exjade therapy was also associated with an increase in the urinary protein/urinary creatinine ratio in a minority of patients. The changes in renal function were not progressive despite the resumption or continuation of Exjade.

Serum transaminase elevations occurred in a small percentage of patients, and drug-related hepatitis developed in at least two patients, one of whom also developed neutropenia.

Uncommon adverse events included cataract development and hearing loss. A few patients have developed neutropenia and thrombocytopenia while receiving Exjade, but the relationship to the drug is uncertain.

Gastrointestinal and renal adverse events appear to be dose-related. Other adverse events appear to have no relation to dose.

There is no information available on Exjade overdosage. There does not appear to be a potential for drug abuse or withdrawal. Exjade does not appear to prolong the QT interval. There is no information available on the effects of Exjade on pregnancy or breast feeding. The applicant's data suggest that Exjade may not impair normal growth and development.

Since Exjade is expected to be administered for an indefinite time period, it will be important to determine the safety consequences of its long-term use on the already identified target organs of toxicity, i.e., the kidney and liver. In addition, the frequency of other uncommon adverse events (ophthalmological, audiological, hematological) will only be accurately determined after a larger population has been exposed to Exjade.

In the studies performed by the applicant in which DFO was used as the comparator, the frequency of gastrointestinal and dermatological symptoms was clearly greater in the Exjade arm. The frequency of other adverse events was similar between the two arms except for the increases in serum creatinine, which occurred only in patients treated with Exjade.

### **Dosing Regimen and Administration**

Because the applicant was unable to demonstrate the efficacy of Exjade in patients with an LIC <7 mg Fe/g dw, and because doses of 5-10 mg/kg/d were clearly ineffective in patients receiving regular blood transfusions as part of the standard treatment for  $\beta$ -thalassemia, recommendations for dosing and administration cannot be stated with certainty. The applicant recommends that Exjade therapy be commenced after the patient has received approximately 20 units of packed red cell transfusions or when there is evidence of iron overload by clinical monitoring (e.g., serum ferritin >1000  $\mu$ g/L). The administration of 20 units of packed red cells would increase total body iron by approximately 4-5 g. In a 50 kg person, this would increase the normal LIC (<1.5 mg Fe/g dry weight) by approximately 8-9 g. The calculated LIC would therefore be in excess of the 7 mg Fe/g dry weight which is the level of iron overload that was successfully treated using Exjade. The degree of iron overload in a child receiving a similar transfusion regimen would be even greater. The use of a serum ferritin level of greater than 1000  $\mu$ g/L to determine initiation of therapy is not well founded even though it is rare for that high a level to be associated with anything other than iron overload.

For patients receiving regular transfusion therapy of 2-4 units of packed red cells per month, the applicant recommends that the initial dose of Exjade should be 20 mg/kg/d. A dose of 30 mg/kg/d is recommended for patients receiving more frequent transfusions and a dose of 10 mg/kg/d is recommended for patients receiving fewer transfusions. These recommendations appear consistent with the data provided in the clinical trials, and provide a margin of safety for the initial dosing.

The applicant recommends that maintenance therapy be determined on the basis of serial observations of serum ferritin and that dose adjustments be made in steps of 5-10 mg/kg/d to achieve a therapeutic goal of either stabilizing or reducing body iron stores. The applicant does not recommend doses of Exjade above 30 mg/kg/d. These recommendations are problematic because, although there is a population relation between LIC and serum ferritin, the dispersion of results and the variability in serial observations are too great for dose determination in an individual. Nonetheless, short of

initial and repeat liver biopsy to determine dosing, serum ferritin appears to be the best currently available guide to dosing decisions, and is, in fact, the measure commonly used in practice. There is little likelihood that the physician or patient community will agree to liver biopsy to guide dosing.

### **Drug-Drug Interactions**

The only drug-drug interaction study performed by the applicant was between Exjade and digoxin, which showed no effect of Exjade on the pharmacological characteristics of digoxin.

### **Special Populations**

For the proposed indication, the effects of Exjade have been adequately studied in subpopulations, including those based on gender and pediatric age. The use of Exjade in non-Caucasian patients in clinical trials is limited. There is little information available on the effects of Exjade in patients over the age of 65 years. Patients with serum creatinine levels above the upper limit of normal were excluded from the trials and the effects of Exjade in patients with renal dysfunction are not known. Patients with serum transaminases >5x ULN were excluded from the trials so the effects of Exjade in patients with serum transaminases >5x ULN or who have other evidence of hepatic dysfunction are not known. Exjade has not been studied in pregnancy or in nursing mothers.