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Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Briefing Document

EXJADE® (desferasirox: ICL670) for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.

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List of abbreviations

CVA	Cerebrovascular accident
DBA	Diamond-Blackfan anemia
DFO	Deferoxamine
dw	Dry weight (for liver biopsy)
LIC	Liver iron content
MRI	Magnetic resonance imaging
NDA	New Drug Application
ODAC	Oncology Drugs Advisory Committee
PMC	Post Marketing Commitments
PRBC	Packed red blood cells
SCD	Sickle cell disease
SPA	Special Protocol Assessment
SQUID	magnetic susceptometry by superconducting quantum interference device
TCD	Transcranial Doppler
ULN	Upper limit of normal

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1 Purpose of document

Recognizing a high unmet medical need, and on the basis of a positive benefit-risk assessment of the data from several clinical trials, Exjade® (ICL670, deferasirox) was approved by the FDA under the accelerated approval regulations on November 2, 2005 for *the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older* (see prescribing information in Appendix 1).

The purpose of this document is to present to the members of the pediatric subcommittee of the Oncology Drugs Advisory Committee (ODAC) the agreements reached with the agency to further document the long term safety and efficacy of Exjade® (chronic therapy) in children. In addition, we also wish to share and seek guidance on plans being developed by the sponsor to address the commitments relevant to the use of Exjade® in pediatric patients.

2 Background information

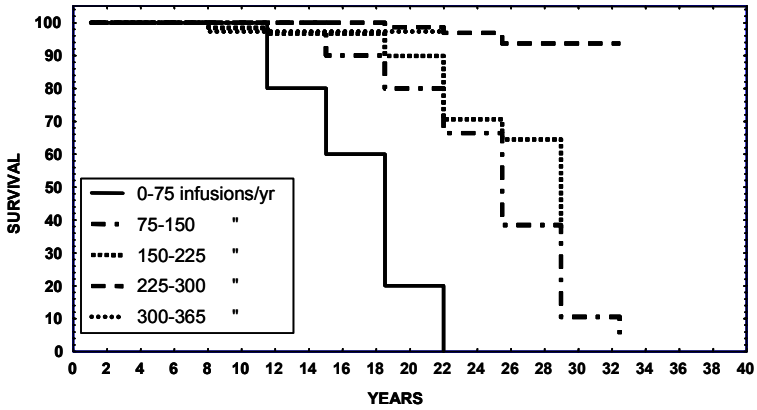
2.1 Background on the disease

Transfusional iron overload: a high unmet medical need

Chronic iron overload represents a serious complication of potentially life-saving regular blood transfusions administered for a variety of congenital and acquired types of anemia. Iron from frequent blood transfusions deposits mainly in the liver, endocrine organs, and heart. The pathologic changes and clinical manifestations associated with progressive iron overload have been best documented in patients with β-thalassemia major where they are already apparent within the first 5 years of life [Iancu 1977; Jean 1984, Olivieri 1997]. In these frequently transfused patients, the total body iron burden is estimated to increase at a rate of 2 to 5 g of iron per year [Olivieri, 1999]. A convincing body of evidence also shows that morbidity and mortality from iron overload affects patients with other disorders requiring long-term blood transfusion [Schafer 1981; Ballas 2001; Olivieri 2001]. Regardless of the underlying disease state, without therapeutic intervention, excess iron leads to tissue damage, ultimately culminating in organ failure and early death [Olivieri 1997].

Deferoxamine mesylate (Desferal®, DFO) was introduced about forty years ago and has been the only approved drug in the United States for the removal of excess iron due to blood transfusions. However, because of a very short half-life, the drug has to be administered by slow continuous subcutaneous infusions, over a period of 8 to 12 hours five to seven nights per week [Porter, 2001]. Several clinical studies have shown that good compliance to this very demanding therapy is critical to the efficacy of therapy and ultimately patients long-term survival (Figure 2-1) [Ehlers 1991; Brittenham 1994; Olivieri 1994; Gabutti 1996; Borgna-Pignatti 2004]. Unfortunately, due to the challenges of administering DFO by prolonged subcutaneous infusion, compliance with therapy is often poor. Therefore, many patients experience morbidity and mortality related to non-compliance, despite the availability of a drug that is otherwise effective in preventing complications associated with iron overload [Cohen, 1987; Arboretti 2001].

Figure 2-1 Relationship of survival to deferoxamine infusions in thalassemia (from Gabutti 1996)



There was therefore a high unmet medical need and this has driven the search for safe and effective oral iron chelators which are easy to administer and thus may enhance compliance.

Iron chelation in β-thalassemia

Medical histories of transfused β-thalassemia patients published before deferoxamine (DFO) became generally available suggest that the liver damage may be detectable as early as 2 years of age [Iancu 1977; Jean 1984]. Without chelation therapy, patients generally develop cirrhosis between the ages of 10 to 15 years, but mild cirrhosis has been observed as early as 8 or 9 years of age [Prati 2004]. Endocrine complications including pituitary and gonadal failure are common even early in life leading to growth failure and delayed development of secondary sexual characteristics. The development of diabetes mellitus by early in the second decade of life is frequent. Cardiac complications, often manifest as congestive heart failure, have a peak incidence between age 10 and 15 years [Engle 1963, Olivieri 1999].

In patients with β-thalassemia, iron chelation therapy is generally initiated very early in life when the body iron burden is clearly increased, as evidenced by a serum ferritin level of greater than 1000 µg/L or after the cumulative administration of 10 to 20 blood transfusions [Gabutti 1996; Porter 2001]. Studies performed after the introduction of DFO demonstrated an improvement in liver pathology, liver function, growth, sexual development and cardiac function in adults and children and adolescents.

Iron chelation in Sickle cell disease

The goal of blood transfusion in SCD is different from that in β-thalassemia major. Regular transfusions are used to decrease the proportion of circulating red cells containing abnormal sickle hemoglobin (HbS and others) and thereby to decrease the risk of developing severe complications such as stroke and acute chest syndrome [Stuart 2004]. Types of transfusions administered to patients with SCD include intermittent or regular transfusions and exchange transfusions.

The main indication for chronic blood transfusion in SCD is for the primary and secondary prevention of cerebro-vascular accidents (CVA) [Stuart 2004]. The peak incidence of CVA in children with SCD is between the ages of 1 and 9 years [Ohene-Frempong K. 1998]. Chronic transfusion has been shown to efficiently prevent CVA in children with abnormal intracranial blood flow measured by transcranial Doppler (TCD) [Adams 1998, Adams 2005] and guidelines for selecting patients for initiating transfusion therapy are available, [NIH 2002]. The age at which transfusion is initiated is variable, however in two large randomized studies the mean age of initiation of transfusion was 7 to 8 years. [Adams 1998, Adams 2005].

Similarly to the standard of care in β-thalassemia, practice guidelines recommend to start iron chelation therapy in chronically transfused SCD patients when serum ferritin is elevated and after the cumulative transfusion of 120 mL/kg PRBC, or approximately one year after the initiation of transfusion therapy [NIH 2002, Pane 2001].

2.2 Exjade®

ICL670 (Exjade®, deferasirox) is an N-substituted bis-hydroxyphenyl-triazole, which represents a new class of tridentate iron chelators with high affinity and selectivity for iron. Biopharmaceutical and pharmacokinetic properties of Exjade® allow administration by the oral route as a once-daily administration and facilitate access to intracellular iron stores.

2.2.1 Regulatory history

FDA recognized the medical need and potential of Exjade® when it granted Exjade® Fast Track Status in February 2003. The full NDA was submitted on April 29, 2005 and priority review was granted in June 2005 and accelerated approval on November 2, 2005. Exjade® received Orphan Drug Designation on November 21, 2002. Although pediatric studies are not required for orphan drugs under the Pediatric Research Equity Act, Novartis recognized the medical need for this drug in the pediatric population and included pediatric patients in the key clinical studies. FDA completed Special Protocol Assessments (SPA) for the designs of the three main clinical studies (Studies 0107, 0108, 0109) in January 2003. Close consideration was given to these SPA comments on the design, conduct, and analysis of these studies as it related to both adult and pediatric patients throughout the development program. The NDA included the overall outcomes of the final analyses for the safety and efficacy data collected from the pediatric population of 292 patients (aged 2 to <16 years) treated with Exjade®. The approved prescribing information provides guidance on the use of Exjade® in pediatrics as well as adults (Appendix 1).

2.2.2 Overview of Exjade® clinical development program

The clinical data on which the marketing approval of Exjade® was based were derived from a large and very comprehensive program bearing in mind that this is a rare orphan indication with significant unmet medical need. Following initial dose-finding phase I and phase II studies, the program enrolled a total of 1005 patients with a range of underlying conditions (including β-thalassemia, SCD, Diamond-Blackfan anemia, and other rare anemias) in four key efficacy and safety studies 0106, 0107, 0108 and 0109 (Table 2-1).

Table 2-1 Exjade® NDA. Summary of key efficacy and safety trials

Study No.	Design	No. of patients	Drug dose and treatment duration*	Objectives
Phase II trials				
0106	Non-comparative trial of ICL670 in pediatric patients with β-thalassemia unable to receive or to tolerate DFO	40 (children)	ICL670 10 mg/kg 1 year duration	Safety
0108	Non-comparative trial of ICL670 in patients with β-thalassemia unable to receive or to tolerate DFO, or with other anemias	184 (adults & children)	ICL670 5, 10, 20 or 30 mg/kg 1 year duration	Efficacy Safety
0109	Open-label, randomized phase II trial of ICL670 vs DFO in patients with SCD and transfusional iron overload	195 (adults & children)	ICL670: 5, 10, 20,or 30 mg/kg DFO: 20-60 mg/kg 1 year duration	Safety Efficacy
Phase III trials				
0107	Open-label, randomized phase III trial of ICL670 vs DFO in patients with β-thalassemia	586 (adults & children)	ICL670 5, 10, 20 or 30 mg/kg DFO 20-60 mg/kg 1 year duration	Efficacy Safety Population PK

*All patients on study at 1 year were eligible for enrollment into extension protocols for each trial

The design of the studies and their overall results are described in details in the briefing book prepared for the meeting of the Blood Products Advisory Committee held on September 29, 2005 (http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4177B1_01.pdf).

2.2.3 Overview of pediatric clinical data with Exjade®

Since the FDA approval in November 2005, no other clinical studies have been completed. However Novartis has started the planning to address the post-approval commitments.

Of the 1005 patients enrolled in these four studies, 468 were pediatric patients aged 2 to <16 years, 292 of whom were treated with ICL670 (Table 2-2). Importantly, 83 patients (8.3%) were in the age range of 2 to < 6 years, of which 52 patients received Exjade®. Among these 292 pediatric patients treated with Exjade®, the underlying anemia was β-thalassemia (n=205), SCD (n=67), Blackfan-Diamond anemia (n=15) or other rare anemias (n=5).

Table 2-2 Number and % of pediatric patients treated with Exjade® by study (n=652)

Exjade® patients	Study 106 N = 40	Study 107 N = 296	Study 108 N = 184	Study 109 N = 132	All patients N = 652
Patients < 16 years	36 (90%)	154 (52%)	35 (19%)	67 (51%)	292 (45%)
Age group					
≥ 2 - < 6 years	7 (17.5%)	30 (10.1%)	11 (6.0%)	4 (3.0%)	52 (8.0%)
6 - < 12 years	13 (32.5%)	67 (22.6%)	11 (6.0%)	30 (22.7%)	121 (18.6%)
12 - < 16 years	16 (40.0%)	57 (19.3%)	13 (7.1%)	33 (25.0%)	119 (18.3%)
16 - < 50 years	4 (10.0%)	142 (48.0%)	99 (53.8%)	63 (47.7%)	308 (47.2%)
50 - < 65 years	0	0	20 (10.9%)	2 (1.5%)	22 (3.4%)
≥ 65 years	0	0	30 (16.3%)	0	30 (4.6%)

The baseline iron burden of these pediatric patients, as measured by LIC or serum ferritin, was high, with levels similar to adults. In children aged 2 to <6 years, the mean LIC was 14.5 mg Fe/g dw, and mean serum ferritin was 2337 µg/L indicating a population at risk of clinical complications [Olivieri 1994]. Reflecting the standard medical practice of blood transfusions in this population, young children aged 2 to <6 years typically received a higher amount of blood transfused per kg body weight in comparison to adults or older children.

Including the additional follow-up included in the 120-day safety update, the mean (±SD) duration of exposure in the different age categories from the total number of 652 patients treated with Exjade® was 19.0±5.1 months in children aged <6 years, 17.8±5.6 months in children 6-<12 years, and 18.2±6.0 months in children aged 12-<16 years, respectively (versus 16.4±6.5 months in adults).

With regards to efficacy, in the comparative Study 0107, which enrolled the largest number of pediatric patients, the changes in LIC and in serum ferritin in relation to dose of Exjade® and DFO were similar across pediatric and adult age groups. Furthermore, data from the comparative Study 0107 and pooled data from studies 0106, 0107, 0108 and 0109 on the dose-response measured as changes in LIC verify that in children age 2 to <6 years doses of 20 and 30 mg/kg were effective in maintaining or reducing iron burden in this intensively transfused patient population (LIC changes of +0.4 ±4.4 (n=16) and -4.1 ±7.1 mg Fe/g dw (n=17), respectively).

With regards to safety, the frequency of adverse reactions with Exjade® was similar across all age groups, with the exception of transient diarrhea which was more common in children age 2 to <6 years. The frequency of elevation of serum creatinine >33% from baseline was similar across all age groups. In the pooled population from studies 0106, 0107, 0108, and 0109 no child aged 2 to < 6 years treated with Exjade® had a clinically relevant increase in serum creatinine (defined as >33% and >ULN on two consecutive occasions). Over the one year duration of the trials, height, growth and sexual maturation were not different between the Exjade® group and the DFO treated groups.

2.2.4 Approval of Exjade® and post-marketing commitments

On the basis of the efficacy and safety data discussed above, the FDA Blood Products Advisory Committee recommended the approval of Exjade® for the treatment of transfusional iron overload on September 29, 2005. Subsequently, the FDA approved Exjade® on

November 2, 2005 for "the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older", with the prescribing information presented in Appendix 1.

Recognizing a high unmet medical need for an effective and more convenient iron chelation therapy, Exjade® was approved under the accelerated approval mechanism. Accordingly, the FDA proposed and Novartis agreed to conduct additional studies to further document long term safety as post-marketing commitments (PMC).

1. Establish a registry for children aged 2 to < 6 years to enroll approximately 200 patients and follow them for 5 years. Data collection will be at least monthly for renal function and blood pressure and yearly for growth and development. Submit your monitoring scheme for our review and comment.
2. Complete the extension portion of Studies 0105E2, 0106E1, 0107E1, 0108E1 (in β-thalassemia), and 0109E1 (in sickle cell disease) for a total of 4 years after the core trial (5 years total in patients initially treated with ICL670, 4 years for patients initially treated with DFO). (Note: study 105E2 was a randomized phase 2 study in adults with β-thalassemia)
3. Conduct a single arm study in patients with congenital or acquired anemias and chronic iron overload to obtain additional data in patients with LIC < 7 treated with Exjade® doses of 20 or 30 mg/kg per day.
4. Provide the full study report, including safety and efficacy datasets, for Study 0109, a study in patients with sickle cell disease.
5. Provide an adequate proposal for assessing iron concentration and cardiac function in patients treated with Exjade®.

Those commitments which have relevance to the use of Exjade® in the pediatric population are detailed in the following section.

3 Post marketing study commitments under the accelerated approval regulation

3.1 Establish a pediatric registry for children aged 2 to <6 years (PMC #1)

This registry is envisioned to be an open-label prospective observational study. The primary objective will be to evaluate the long-term safety of Exjade® in an unselected population of children aged 2 to <6 years at study entry with chronic iron overload related to blood transfusions used in the treatment of β-thalassemia or SCD.

Iron overload qualifying for study entry will be defined in accordance with established patients management guidelines regarding iron chelation therapy as a cumulative blood transfusion history of ≥100 mL/kg of packed red blood cells (approximately 20 units for a 40 kg patient) and a serum ferritin consistently >1000 µg/L.

Patients will be treated with Exjade® according to the investigator's judgment and in accordance with the local Exjade® prescribing information. Patients will be followed-up for

up to 5 years. Beside monitoring of adverse events, safety assessments will include monthly monitoring of renal function and blood pressure, and yearly monitoring of growth and sexual development, as requested by FDA.

The proposed sample size is 200 patients, in order to have approximately 100 patients evaluable at the end of the 5-years study period. This number is proposed on the basis of feasibility and pragmatic considerations taking into account the relative rarity of the disease in this age group.

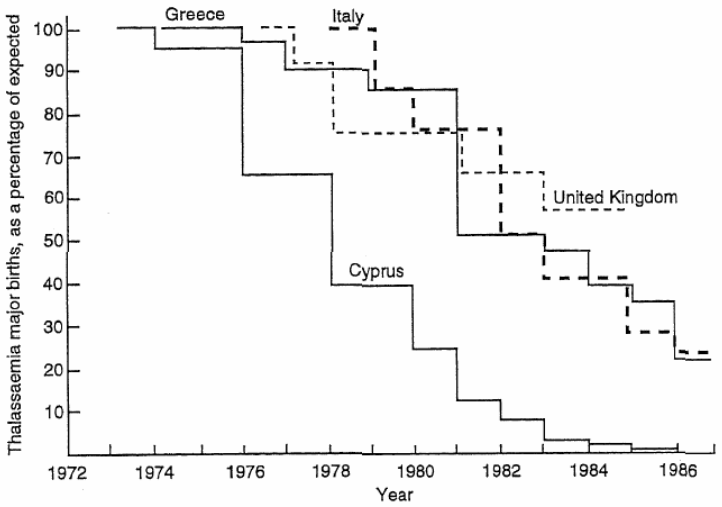
Summary statistics will be performed on all dosing, growth and safety parameters. This information will be presented in descriptive format. All subsequent analyses will be descriptive against change from baseline values.

Challenges raised by this commitment

The primary challenge raised by this commitment is the rarity of children <6 years with thalassemia or SCD requiring iron chelation therapy. The reasons are twofold.

Firstly, the incidence of births of infants diagnosed with β-thalassemia is declining as a result of the implementation of systematic health education programs and prenatal screening programs in several countries with a high incidence of thalassemia [Olivieri 1999]. For example (Figure 3-1), in Cyprus, Greece, Italy and UK, the births of thalassemia children have been reduced by more than 90% in recent years by intensive prenatal screening programs [Orkin 2003, Petrou 1995]. Against this background, the enrollment of a total of 83 children aged <6 years across all trials in the NDA represent a significant achievement.

Figure 3-1 Decrease in the births of infants with β-thalassemia in high prevalence countries with the implementation of active screening programs



(From Petrou et al., Prenat Diagn., 1995, 15: 1275-95

Secondly, the data summarized above in Section 2.1 suggest that when indicated on the basis of abnormal TCD, chronic transfusion for the prevention of CVA in SCD is probably only

rarely initiated before the age of 4 to 6 years, and subsequent iron chelation therapy rarely initiated before the age of 5 to 7 years. This is actually reflected by the demographics of the SCD patients enrolled in the Exjade® program in Study 0109, in which 51% of patients were aged <16 years but only 3% were children aged <6 years (and 22.7% and 25.0% aged 6-<12 years and 12-<16 years, respectively) (Table 2-1). Taken together, these data suggest that young SCD patients <6 years of age are likely to be a minority population in the registry.

Therefore, the enrollment of a total of 200 patients may eventually be challenging. Accordingly, the registry will likely be run as a multicenter and multinational study, including countries without systematic prenatal screening programs. In addition, other ongoing studies are open for the enrollment of pediatric patients and may provide additional information. It might be considered to integrate these data with the registry data in order to maximize the likelihood to obtain the desired patients exposure.

Advice from the pediatric ODAC subcommittee on these points would be appreciated.

3.2 Collect long-term safety and efficacy data in ongoing trials (PMC #2)

All study protocols for studies 0106 E1, 0107 E1, 0108 E1 and 0109 E1 have been amended to extend the duration of these extension studies to 4 years in addition to the one year of the preceding core phase. As agreed, the amendments have been submitted to FDA on 31st January, 2006. All patients enrolled into the extension studies are treated with Exjade®. In the randomized studies 0107E1 and 0109E1, patients originally randomized to DFO into the core trials were all offered the possibility to be treated with Exjade® into the extension studies.

All safety parameters that were included in the original protocols will continue to be monitored during the additional 4 years, including specific pediatric assessments of growth parameters, school attendance and the development of puberty.

Overall, after completing the one-year preceding core study, a total of 414 pediatric patients <16 years are currently entered into the extension trials as listed in Table 3-1 and will contribute to the generation of long-term safety and efficacy data. Of the 414 pediatric patients, 72 were <6 years of age at study entry (28 were previously treated with DFO in studies 107 and 109).

Table 3-1 Number of pediatric patients enrolled in long-term extension studies

	Number of pediatric patients < 16 years of age at study entry		
	Original treatment assignment in the corresponding core trial		
	Exjade®	DFO	All patients
Study 0106 E1	35	-	35
Study 0108 E1	32	-	32
Study 0109 E1	59	29	88
Study 0107 E1	128	131	259
All Studies	254	160	414

3.3 Conduct single arm study to obtain additional data in patients with LIC <7 treated with Exjade® doses of 20 or 30 mg/kg per day. (PMC#3)

A single arm study is planned to address this request which will enroll adult and pediatric patients with congenital or acquired anemias and low iron burden from chronic transfusions. The study will examine efficacy (serum ferritin changes) and safety of Exjade® administered at doses of 10, 20 or 30 mg/kg/day based on transfusion frequency, with dose adjustments based upon serum ferritin trends. It is planned to recruit up to 250 patients, and the core study will last 1 year, with possible subsequent extensions. Pediatric patients of 2 years and older will be permitted to be enrolled and pediatric safety measures will be assessed. The protocol for this study is in development and will be submitted to the FDA by June 2006.

3.4 Provide the final study report of the sickle cell disease comparative trial (PMC #4)

The final study report of this one-year randomized phase II study comparing Exjade® to DFO treatment in adult and pediatric patients with SCD has been completed as agreed and sent to the FDA (January 31st, 2006). The conclusions of this study confirm and extend the data available from the NDA and provide further support to the efficacy and safety of Exjade®. No new safety findings emerged from this study.

This study enrolled 195 patients (n=132 Exjade®, n=63 DFO) with SCD, of which 50.3% were aged <16 years at study entry. About 38% of patients had not received prior iron chelation before study entry. All LIC evaluations were performed by SQUID.

The average transfusional iron intake was similar for DFO and Exjade® (0.21 ± 0.13 and 0.23 ± 0.12 mg/kg/day, respectively) and lower than in β-thalassemia patients in study 0107 (0.40 ± 0.11 mg/kg/day).

With regards to efficacy, with average Exjade® doses of 18.2, 14.6, 19.0 and 17.5 mg/kg, respectively, mean LIC responses were similar in all age groups (Table 3-1) and were comparable to those seen for DFO (one year data). The average DFO doses were 30.0, 36.7, 34.4 and 38.6 mg/kg, with an average DFO to Exjade® dosing ratio around 2:1 in all dose groups. Overall, as for studies 0107 and 0108, mean doses of about 20 mg/kg/day were able to approximately maintain levels of body iron burden.

Table 3-2 Study 0109 - Change in LIC by age group (one year data)*

	Exjade® (n=113)		DFO (n=54)	
Age group	**n**	**(mean ±SD)**	**n**	**(mean ±SD)**
Change in LIC (in mg Fe/g dw)				
2 - < 6 years	3	-2.9 ± 1.7	2	0.5 ± 0.4
6 - < 12 years	29	-0.6 ± 2.5	15	0.1 ± 1.3
12 - < 16 years	29	-0.6 ± 3.2	11	-0.2 ± 1.7
≥ 16 years	52	-2.0 ± 3.4	26	-1.5 ± 3.3

*PP-2 population: patients with a baseline and EOS data

3.5 Evaluation of cardiac iron concentration (PMC #5)

The development of cardiomyopathy related to iron overload typically occurs in the second decade of life or later [Engle 1963, Olivieri 1999]. However, only limited data are available about the relationship between the development of overt cardiac failure and actual cardiac iron content. Several non-invasive, investigational MRI-based methods are currently being developed to more accurately determine cardiac iron status. Novartis is committed to initiate studies to prospectively evaluate the use of these methods in patients treated with Exjade® and correlate the findings with measurement of left ventricular ejection fraction (LVEF). A draft protocol for such a study has already been submitted to the FDA for review (January 31st, 2006). Even though these studies will be performed in adult patients in whom most of the current knowledge in this field has been accumulated, they may provide useful insights into the prevention of iron overload cardiomyopathy using Exjade® in children.

4 Conclusion

Overall, it is important to note that the current prescribing information presented in Appendix 1 is based on a large safety and efficacy database (including a large number of pediatric patients) for an orphan designated product and indication and its approval has documented a favorable benefit-to-risk assessment.

Based on the Blood Products Advisory Committee and FDA discussions, Novartis recognizes the need for assessing long-term safety and efficacy of Exjade®, particularly in pediatric patients. Studies either ongoing or planned in the context of the post marketing commitments agreed with the FDA should provide additional information that would be useful for physicians and prescribers. Novartis continues to diligently move forward to meet its obligations for post-marketing commitments.

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Appendix 1: Exjade® prescribing information

T2005-65

EXJADE®

(deferasirox)

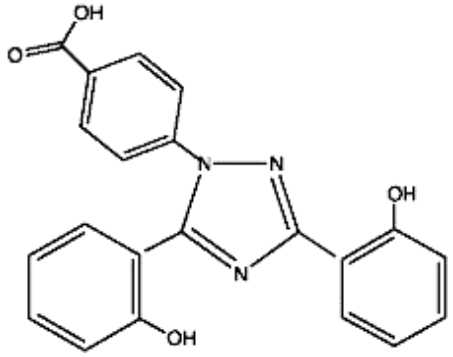
Tablets for Oral Suspension

Rx only

Prescribing Information

DESCRIPTION

EXJADE® (deferasirox) is an iron chelating agent. EXJADE tablets for oral suspension contain 125 mg, 250 mg, or 500 mg deferasirox. Deferasirox is designated chemically as 4-[3,5-Bis (2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]-benzoic acid and its structural formula is



Deferasirox is a white to slightly yellow powder. Its molecular formula is $C_{21}H_{15}N_3O_4$ and its molecular weight is 373.4.

Inactive Ingredients: Lactose monohydrate (NF), crospovidone (NF), povidone (K30) (NF), sodium lauryl sulphate (NF), microcrystalline cellulose (NF), silicon dioxide (NF), and magnesium stearate (NF).

CLINICAL PHARMACOLOGY

General

Mechanism of Action/Pharmacodynamics

EXJADE® (deferasirox) is an orally active chelator that is selective for iron (as Fe^{3+}). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Although deferasirox has very low affinity for zinc and copper there are variable decreases in the serum concentration of these trace metals after the administration of deferasirox. The clinical significance of these decreases is uncertain.

Pharmacodynamic effects tested in an iron balance metabolic study showed that deferasirox (10, 20 and 40 mg/kg per day) was able to induce a mean net iron excretion (0.119, 0.329 and 0.445 mg Fe/kg body weight per day, respectively) within the clinically relevant range (0.1-0.5 mg/kg per day). Iron excretion was predominantly fecal.

The effect of 20 and 40 mg/kg of deferasirox on QT interval was evaluated in a single-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg), parallel group study in 182 healthy male and female volunteers aged 18-65 years. No evidence of prolongation of the QTc interval was observed in this study.

Pharmacokinetics

Absorption

EXJADE is absorbed following oral administration with median times to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. The C_{max} and AUC of deferasirox increase approximately linearly with dose after both single administration and under steady-state conditions. Exposure to deferasirox increased by an accumulation factor of 1.3 to 2.3 after multiple doses. The absolute bioavailability (AUC) of deferasirox tablets for oral suspension is 70% compared to an intravenous dose.

Distribution

Deferasirox is highly (~99%) protein bound almost exclusively to serum albumin. The percentage of deferasirox confined to the blood cells was 5% in humans. The volume of distribution at steady state (V_{ss}) of deferasirox is 14.37 ± 2.69 L in adults.

Metabolism

Glucuronidation is the main metabolic pathway for deferasirox, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. Deferasirox is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3. CYP450-catalyzed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). No evidence for induction or inhibition of enzymes at therapeutic doses has been observed.

Excretion

Deferasirox and metabolites are primarily (84% of the dose) excreted in the feces. Renal excretion of deferasirox and metabolites is minimal (8% of the administered dose). The mean elimination half-life ($t_{1/2}$) ranged from 8 to 16 hours following oral administration.

Special Populations

Renal Insufficiency

Deferasirox is minimally (8%) excreted via the kidney. EXJADE has not been studied in patients with renal impairment. (See also PRECAUTIONS, Laboratory Tests, and ADVERSE REACTIONS.)

Hepatic Insufficiency

Deferasirox is principally excreted by glucuronidation and is minimally (8%) metabolized by oxidative cytochrome P450 enzymes. EXJADE has not been studied in patients with hepatic impairment. EXJADE treatment has been initiated in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range. The pharmacokinetics of deferasirox were not influenced by such transaminase levels.

Pediatric/Geriatric Patients

Following oral administration of single or multiple doses, systemic exposure of adolescents and children to deferasirox was less than in adult patients. In children <6 years of age, systemic exposure was about 50% lower than in adults. (See PRECAUTIONS, Pediatric Use.) The pharmacokinetics of deferasirox have not been studied in geriatric patients (65 years of age or older).

Gender

Females have a moderately lower apparent clearance (by 17.5%) for deferasirox compared to males.

CLINICAL STUDIES

The primary efficacy study, Study 1, was a multicenter, open-label, randomized, active comparator control study to compare EXJADE® (deferasirox) and deferoxamine in patients with β-thalassemia and transfusional hemosiderosis. Patients ≥2 years of age were randomized in a 1:1 ratio to receive either oral EXJADE at starting doses of 5, 10, 20 or 30 mg/kg once daily or subcutaneous Desferal® (deferoxamine) at starting doses of 20 to 60 mg/kg for at least 5 days per week based on LIC (liver iron concentration) at baseline (2-3, >3-7, >7-14 and >14 mg Fe/g dry weight). Patients randomized to deferoxamine who had LIC values <7 mg Fe/g dry weight were permitted to continue on their prior deferoxamine dose, even though the dose may have been higher than specified in the protocol.

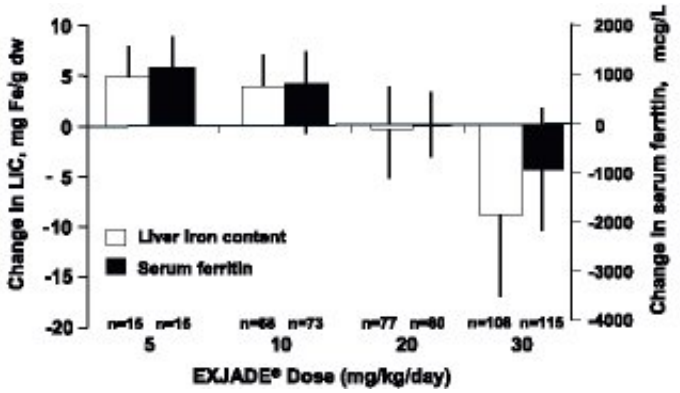
Patients were to have a liver biopsy at baseline and end of study (after 12 months) for LIC. The primary efficacy endpoint was defined as a reduction in LIC of ≥3 mg Fe/g dry weight for baseline values ≥10 mg Fe/g dry weight, reduction of baseline values between 7 and <10 to <7 mg Fe/g dry weight, or maintenance or reduction for baseline values <7 mg Fe/g dry weight.

A total of 586 patients were randomized and treated, 296 with EXJADE and 290 with deferoxamine. The mean age was 17.1 years (range, 2-53 years); 52% were females and 88% were Caucasian. The primary efficacy population consisted of 553 patients (EXJADE n=276; deferoxamine n=277) who had LIC evaluated at baseline and 12 months or discontinued due to an adverse event. The percentage of patients achieving the primary endpoint was 52.9% for EXJADE and 66.4% for deferoxamine. The relative efficacy of EXJADE to deferoxamine cannot be determined from this study.

In patients who had an LIC at baseline and at end of study, the mean change in LIC was -2.4 mg Fe/g dry weight in patients treated with EXJADE and -2.9 mg Fe/g dry weight in patients treated with deferoxamine.

Reduction of LIC and serum ferritin were observed with EXJADE doses of 20 to 30 mg/kg. EXJADE doses below 20 mg/kg per day failed to provide consistent lowering of LIC and serum ferritin levels (Figure 1). Therefore, a starting dose of 20 mg/kg per day is recommended. (See DOSAGE AND ADMINISTRATION.)

Figure 1. Changes in Liver Iron Concentration and Serum Ferritin Following EXJADE® (5 to 30 mg/kg per day) in Study 1



Study 2 was an open-label, non-comparative trial of efficacy and safety of EXJADE given for 1 year to patients with chronic anemias and transfusional hemosiderosis. Similar to Study 1, patients received 5, 10, 20, or 30 mg/kg per day of EXJADE based on baseline LIC.

A total of 184 patients were treated in this study: 85 patients with β-thalassemia and 99 patients with other congenital or acquired anemias (myelodysplastic syndromes, n=47; Diamond-Blackfan syndrome, n=30; other, n=22). Nineteen percent of patients were <16 years of age and 16% were ≥65 years of age. There was a reduction in the absolute LIC from baseline to end of study (-4.2 mg Fe/g dry weight).

Study 3 assessed the safety of EXJADE in patients with sickle cell disease and transfusional hemosiderosis. Patients were randomized to EXJADE at doses of 5, 10, 20, or 30 mg/kg per day or subcutaneous deferoxamine at doses of 20 to 60 mg/kg per day for 5 days per week according to baseline LIC. See ADVERSE REACTIONS section for safety experience with EXJADE in patients with sickle cell disease.

INDICATIONS AND USAGE

EXJADE® (deferasirox) is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.

CONTRAINDICATIONS

Use of EXJADE® (deferasirox) is contraindicated in patients with hypersensitivity to deferasirox or to any other component of EXJADE.

WARNINGS

Renal

EXJADE® (deferasirox)-treated patients experienced dose-dependent increases in serum creatinine. These increases occurred at a greater frequency compared to deferoxamine-treated patients (38% vs. 15%, respectively) in Study 1. Most of the creatinine elevations remained within the normal range. Serum creatinine should be assessed before initiating therapy and should be monitored monthly thereafter. Dose reduction, interruption, or discontinuation should be considered for elevations in serum creatinine. In the clinical trials, for increases of serum creatinine on two consecutive measures (>33% in patients >15 years of age or >33% and greater than the age-appropriate upper limit of normal in patients <15 years of age), the daily dose of EXJADE was reduced by 10 mg/kg. Patients with serum creatinine above the upper limit of normal were excluded from clinical trials.

In clinical trials, urine protein was measured monthly. Intermittent proteinuria (urine protein/creatinine ratio >0.6 mg/mg) occurred in 18.6% of EXJADE-treated patients compared to 7.2% of deferoxamine-treated patients in Study 1. Although no patients were discontinued from EXJADE in clinical trials up to 1 year due to proteinuria, close monitoring is recommended. The mechanism and clinical significance of the proteinuria are uncertain.

Hepatic

In Study 1, 4 patients discontinued EXJADE because of hepatic abnormalities (drug-induced hepatitis in 2 patients and increased serum transaminases in 2 additional patients). Liver function tests should be monitored monthly during EXJADE treatment and dose modifications considered for severe or persistent elevations.

Special Senses

Auditory disturbances (high frequency hearing loss, decreased hearing), and ocular disturbances (lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders) have been reported at a frequency of <1% with EXJADE therapy in the clinical trials. Auditory and ophthalmic testing (including slit lamp examinations and dilated fundoscopy) are recommended before the start of EXJADE treatment and thereafter at regular intervals (every 12 months). If disturbances are noted, dose reduction or interruption should be considered.

PRECAUTIONS

General

Skin rashes may occur during EXJADE® (deferasirox) treatment. For rashes of mild to moderate severity, EXJADE may be continued without dose adjustment, since the rash often resolves spontaneously. In severe cases, EXJADE may be interrupted. Reintroduction at a lower dose with escalation may be considered in combination with a short period of oral steroid administration.

Information for Patients

EXJADE should be taken once daily on an empty stomach at least 30 minutes prior to food, preferably at the same time every day. The tablets should not be chewed or swallowed whole. The tablets should first be completely dispersed in water, orange juice, or apple juice, and the resulting suspension drunk immediately. After swallowing the suspension, any residue should be resuspended in a small volume of the liquid and swallowed.

Patients should be cautioned not to take aluminum-containing antacids and EXJADE simultaneously.

Because auditory and ocular disturbances have been reported with EXJADE, patients should have auditory and ophthalmic testing before starting EXJADE treatment and thereafter at regular intervals. (See WARNINGS, Special Senses.)

Patients experiencing dizziness should exercise caution when driving or operating machinery (see ADVERSE REACTIONS).

Laboratory Tests

Serum ferritin should be measured monthly to assess response to therapy and to evaluate for the possibility of overchelation of iron. If the serum ferritin falls consistently below 500 mcg/L, consideration should be given to temporarily interrupting therapy with EXJADE. (See DOSAGE AND ADMINISTRATION.)

In the clinical studies, the correlation coefficient between the serum ferritin and LIC was 0.63. Therefore, changes in serum ferritin levels may not always reliably reflect changes in LIC.

Laboratory monitoring of renal and hepatic function should be performed. (See WARNINGS.)

Drug Interactions

The concomitant administration of EXJADE and aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron, EXJADE should not be taken with aluminum-containing antacid preparations.

In healthy volunteers, EXJADE had no effect on the pharmacokinetics of digoxin. The effect of digoxin on EXJADE pharmacokinetics has not been studied.

The concomitant administration of EXJADE and vitamin C has not been formally studied. Doses of vitamin C up to 200 mg were allowed in clinical studies without negative consequences.

The interaction of EXJADE with hydroxyurea has not been formally studied. No inhibition of deferasirox metabolism by hydroxyurea is expected based on the results of an *in vitro* study.

EXJADE should not be combined with other iron chelator therapies as safety of such combinations has not been established.

Drug/Food Interactions

The bioavailability (AUC) of deferasirox was variably increased when taken with a meal. Deferasirox should be taken on an empty stomach 30 minutes before eating.

EXJADE tablets for oral suspension can be dispersed in water, orange juice, or apple juice.

Carcinogenicity/Mutagenesis/Impairment of Fertility

A 104-week oral carcinogenicity study in Wistar rats showed no evidence of carcinogenicity from deferasirox at doses up to 60 mg/kg per day (about 0.48 times the recommended human oral dose based on body surface area). A 26-week oral carcinogenicity study in p53 (+/-) transgenic mice has shown no evidence of carcinogenicity from deferasirox at doses up to 200 mg/kg per day (about 0.81 times the recommended human oral dose based on body surface area) in males and 300 mg/kg per day (about 1.21 times the recommended human oral dose based on body surface area) in females.

Deferasirox was negative in the Ames test and chromosome aberration test with human peripheral blood lymphocytes. It was positive in 1 of 3 *in vivo* oral rat micronucleus tests.

Deferasirox at oral doses up to 75 mg/kg per day (about 0.6 times the recommended human oral dose based on body surface area) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

Pregnancy,

Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in pregnant rats at oral doses up to 100 mg/kg per day (about 0.8 times the recommended human oral dose based on body surface area) and in pregnant rabbits at oral doses up to 50 mg/kg per day (about 0.8 times the recommended human oral dose based on body surface area). These studies have revealed no evidence of impaired fertility or harm to the fetus due to deferasirox. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, deferasirox should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether deferasirox is excreted in human milk. Deferasirox and its metabolites were excreted in breast milk of rats following a 10 mg/kg dose (about 0.08 times the recommended human oral dose based on body surface area). Because many drugs are excreted in human milk, caution should be exercised when deferasirox is administered to a nursing woman.

Pediatric Use

Of the 700 patients who received EXJADE during clinical trials, 292 were pediatric patients 2 to <16 years of age with various congenital and acquired anemias, including 52 patients age 2 to <6 years, 121 patients age 6 to <12 years and 119 patients age 12 to <16 years. Seventy

percent of these patients had β-thalassemia. Children between the ages of 2 to <6 years have a systemic exposure to EXJADE approximately 50% of that of adults (see CLINICAL PHARMACOLOGY). However, the safety and efficacy of EXJADE in pediatric patients was similar to that of adult patients, and younger pediatric patients responded similarly to older pediatric patients. The recommended starting dose and dosing modification are the same for children and adults. (See CLINICAL STUDIES, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION.)

During the 1 year study, the growth and development were within normal limits.

Geriatric Use

EXJADE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Thirty patients ≥65 years of age were included in clinical trials of EXJADE. The majority of these patients had myelodysplastic syndrome (MDS, n=27; other anemias, n=3). In general, caution should be used in elderly patients due to the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

A total of 700 patients were treated with EXJADE® (deferasirox) in therapeutic studies lasting for 48 weeks in adult and pediatric patients. These 700 patients included 469 with β-thalassemia, 99 with rare anemias, and 132 with sickle cell disease. Of these patients, 45% were male, 70% were Caucasian and 292 patients were <16 years of age. In the sickle cell disease population, 89% of patients were Black. Four hundred sixty-nine patients (403 β-thalassemia and 66 rare anemias) were entered into extensions of the original clinical protocols. In ongoing extension studies, median durations of treatment were 85 to 143 weeks.

The most frequently occurring adverse events in the therapeutic trials of EXJADE were diarrhea, vomiting, nausea, headache, abdominal pain, pyrexia, cough, and an increase in serum creatinine. Gastrointestinal symptoms, increases in serum creatinine, and skin rash were dose related.

Table 1 displays adverse events occurring in >5% of patients in either treatment group in Study 1. Abdominal pain, nausea, vomiting, diarrhea, and skin rashes were the most frequent adverse events reported with a suspected relationship to EXJADE.

Table 1 Adverse Events Occurring in >5% of β-Thalassemia Patients in Study 1

Preferred Term	EXJADE® N=296 n (%)	Deferoxamine N=290 n (%)
Pyrexia	56 (18.9)	69 (23.8)
Headache	47 (15.9)	59 (20.3)
Abdominal Pain	41 (13.9)	28 (9.7)
Cough	41 (13.9)	55 (19.0)
Nasopharyngitis	39 (13.2)	42 (14.5)
Diarrhea	35 (11.8)	21 (7.2)
Creatinine Increased*	33 (11.1)	0 (0)
Influenza	32 (10.8)	29 (10.0)
Nausea	31 (10.5)	14 (4.8)
Pharyngolaryngeal Pain	31 (10.5)	43 (14.8)
Vomiting	30 (10.1)	28 (9.7)
Respiratory Tract Infection	28 (9.5)	23 (7.9)
Bronchitis	27 (9.1)	32 (11.0)
Rash	25 (8.4)	9 (3.1)
Abdominal Pain Upper	23 (7.8)	15 (5.2)
Pharyngitis	23 (7.8)	30 (10.3)
Arthralgia	22 (7.4)	14 (4.8)
Acute Tonsillitis	19 (6.4)	15 (5.2)
Fatigue	18 (6.1)	14 (4.8)
Rhinitis	18 (6.1)	22 (7.6)
Back Pain	17 (5.7)	32 (11.0)
Ear Infection	16 (5.4)	7 (2.4)
Urticaria	11 (3.7)	17 (5.9)

*Includes 'blood creatinine increased' and 'blood creatinine abnormal' which were reported as adverse events. Also see Table 2 .

In Study 1, 113 patients treated with EXJADE had increases in serum creatinine >33% above baseline on 2 separate occasions (Table 2). Twenty-five patients required dose reductions. Increases in serum creatinine appeared to be dose related. (See WARNINGS, Renal.) Seventeen patients developed elevations in SGPT/ALT levels >5 times the upper limit of normal at 2 consecutive visits. Two patients had liver biopsy proven drug-induced hepatitis and both discontinued EXJADE therapy. (See WARNINGS, Hepatic.) Two additional patients, who did not have elevations in SGPT/ALT >5 times the upper limit of normal, discontinued EXJADE because of increased SGPT/ALT. Increases in transaminases did not appear to be dose related.

Table 2 Number (%) of Patients with Increases in Serum Creatinine or SGPT/ALT in Study 1

Laboratory Parameter	EXJADE® N=296 n (%)	Deferoxamine N=290 n (%)
Serum Creatinine		
Creatinine >33% and <ULN at ≥2 consecutive post-baseline visits	113 (38.2)	41 (14.1)
Creatinine increase >33% and >ULN at ≥2 consecutive post-baseline visits	7 (2.4)	1 (0.3)
SGPT/ALT		
SGPT/ALT >5 x ULN at ≥2 post-baseline visits	25 (8.4)	7 (2.4)
SGPT/ALT >5 x ULN at ≥2 consecutive post-baseline visits	17 (5.7)	5 (1.7)

Adverse events that led to discontinuations included abnormal liver function tests (2 patients) and drug-induced hepatitis (2 patients), skin rash, glycosuria/proteinuria, Henoch Schönlein purpura, hyperactivity/insomnia, drug fever, and cataract (1 patient each).

In the overall population of 700 patients, uncommon adverse reactions (0.1% to 1%) included gastritis, edema, sleep disorder, pigmentation disorder, dizziness, anxiety, maculopathy, cholelithiasis, pyrexia, fatigue, pharyngolaryngeal pain, early cataract and hearing loss (see PRECAUTIONS). Adverse events which most frequently led to dose interruption or dose adjustment were rash, gastrointestinal disorders, infections, increased serum creatinine, and increased serum transaminases.

OVERDOSAGE

There have been no reports of acute overdose with EXJADE® (deferasirox). Single doses up to 80 mg/kg in iron overloaded β-thalassemic patients have been tolerated with nausea and diarrhea noted. In healthy volunteers, single doses of up to 40 mg/kg were tolerated. There is no specific antidote for EXJADE. In case of overdose, induce vomiting and gastric lavage.

DOSAGE AND ADMINISTRATION

It is recommended that therapy with EXJADE® (deferasirox) be started when a patient has evidence of chronic iron overload, such as the transfusion of approximately 100 mL/kg of packed red blood cells (approximately 20 units for a 40 kg patient) and a serum ferritin consistently >1000 mcg/L.

Starting Dose

The recommended initial daily dose of EXJADE is 20 mg/kg body weight.

Maintenance

After commencing initial therapy, it is recommended that serum ferritin be monitored every month and the dose of EXJADE adjusted if necessary every 3 to 6 months based on serum

ferritin trends. Dose adjustments should be made in steps of 5 or 10 mg/kg and should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). If the serum ferritin falls consistently below 500 mcg/L, consideration should be given to temporarily interrupting therapy with EXJADE. Doses of EXJADE should not exceed 30 mg/kg per day since there is limited experience with doses above this level.

Administration Instructions

EXJADE should be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. Tablets should not be chewed or swallowed whole. EXJADE should not be taken with aluminum-containing antacid products. Doses (mg/kg) should be calculated to the nearest whole tablet. Tablets should be completely dispersed by stirring in water, orange juice, or apple juice until a fine suspension is obtained. Doses of <1 g should be dispersed in 3.5 ounces of liquid and doses of >1 g in 7.0 ounces of liquid. After swallowing the suspension, any residue should be resuspended in a small volume of liquid and swallowed.

HOW SUPPLIED

EXJADE® (deferasirox) Tablets for Oral Suspension

125 mg

Off-white, round, flat tablet with beveled edge and imprinted with "J" and "125" on one side and "NVR" on the other.

Bottles of 30 tablets ……..……(NDC 0078-0468-15)

250 mg

Off-white, round, flat tablet with beveled edge and imprinted with "J" and "250" on one side and "NVR" on the other.

Bottles of 30 tablets ……..……(NDC 0078-0469-15)

500 mg

Off-white, round, flat tablet with beveled edge and imprinted with "J" and "500" on one side and "NVR" on the other.

Bottles of 30 tablets ……..……(NDC 0078-0470-15)

Storage

Store at 25°C (77°F). Excursions permitted to 15–30°C (59–86°F). [see USP Controlled Room Temperature]. Protect from moisture.

Manufactured by:

Novartis Pharma Stein AG

Stein, Switzerland

Distributed by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

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