Session II:

Exjade® Phase 4 requirements

- **Exjade ® (deferasirox) Tablets for Oral Suspension (accelerated approval Nov. 2, 2005)**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-882

Novartis Pharmaceuticals Corporation
Attention: Susan P. Nemeth, Ph.D.
One Health Plaza
Hanover, NJ 07936-1080

Dear Dr. Nemeth:

Please refer to your new drug application (NDA) dated April 29, 2005, received May 2, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exjade® (deferasirox) Tablets for Oral Suspension.

We acknowledge receipt of your submissions dated May 10, May 23, May 27, June 29, July 8, July 11, July 12, July 28, August 15, August 29, September 16, September 20, October 21, October 27, October 31, November 1, and November 2, 2005.

This new drug application provides for the use of Exjade® (deferasirox) Tablets for Oral Suspension for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.

We completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed labeling text and required patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted November 2, 2005) and submitted labeling (immediate container labels submitted October 27, 2005**)**. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-882**." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your

postmarketing study commitments specified in your submission dated November 2, 2005. These commitments, along with any completion dates agreed upon, are listed below.

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.

   Protocol Submission: by June 30, 2006
   Study Start: by December 31, 2006
   Final Report Submission: by June 30, 2012

2. Complete the extension portion of Studies 0105E2, 0106E1, 0107E1, 0108E1, and 0109E1 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).

   Amendment Submission: by January 31, 2006
   Study Start: N/A (ongoing)
   Final Report Submission: by June 30, 2009

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.

   Protocol Submission: by June 30, 2006
   Study Start: by December 31, 2006
   Final Report Submission: by March 31, 2010

4. Provide the full study report, including safety and efficacy datasets, for Study 0109, a study in patients with sickle cell disease.

   Final Report Submission: by January 31, 2006

5. Provide an adequate proposal for assessing iron concentration and cardiac function in patients treated with Exjade®.

   Protocol Submission: by January 31, 2006
   Study Start: by April 30, 2006
   Final Study Report: by June 30, 2008

Submit final study reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing study commitments must be clearly designated "**Subpart H Postmarketing Study Commitments**."

In addition, we note your following postmarketing study commitments, specified in your submission dated November 2, 2005, that are not a condition of the accelerated approval. These commitments are listed below:

6. Complete a study to collect safety and efficacy data for Exjade® in patients with elevated baseline serum creatinine (≥ 2X ULN) in patients with low or intermediate risk MDS (e.g., Study US03, amended to include patients with baseline serum creatinine values up to 2X ULN). Duration of followup on Exjade® should be at least 3 years.

   Amendment Submission: by January 31, 2006
   Study Start: by N/A (ongoing)
   Final Report Submission: by December 31, 2009

7. Conduct a single dose pharmacokinetics study of Exjade® in subjects with hepatic impairment.

   Protocol Submission: by March 31, 2006
   Study Start: by June 30, 2006
   Final Report Submission: by June 30, 2007.

8. Conduct a drug-drug interaction study with midazolam to investigate the potential of Exjade® to inhibit CYP4503A4.

   Protocol Submission: by March 31, 2006
   Study Start: by June 30, 2006
   Final Report Submission: by June 30, 2007

9. Complete study of long-term follow-up (3 years) in 150 patients with myelodysplastic syndromes (MDS) receiving Exjade® to evaluate safety (including cardiac, hepatic, endocrine and renal) and hematologic and clinical benefit of Exjade® in these patients.

   Amendment Submission: by January 31, 2006
   Study Start: N/A (ongoing)
   Final Report Submission: by December 31, 2009

10. Conduct an ophthalmologic study in patients receiving Exjade®. Examinations should include distance visual acuity, applanation tonometry, lens photography, and wide angle fundus photography of retina and optic nerve and should be done at baseline (prior to Exjade® initiation) and at six month intervals. At least 60 patients should complete 2 years of follow-up.

    Protocol Submission: by June 30, 2006
    Study Start: by December 31, 2006
    Final Report Submission: by March 31, 2010

11. Adequately address (b)(4) in the drug substance. To qualify the presence of this impurity of (b)(4) conduct a 4-week repeated dose oral toxicity study with (b)(4) in rats and de--------te that the no effect dose is at least (b)(4) i.e., ≥10 fold-------- concentration than the proposed qualification level (b)(4). Th(b)(b)(4) hould employ (b)(4). (Refer to the ICH Q3A document entitled, "---------- on Impurities in New Drug---------- February 2003).

    Protocol Submission: by January 31, 2006
    Study Start: by May 31, 2006
    Final Study Submission: by December 31, 2006

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Division of Drug Marketing, Advertising and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Although not required, we have the following additional recommendations/requests:

- You are planning a one year trial (study 2409) that will examine the efficacy and safety of Exjade® in about 1500 patients with chronic iron overload due to blood transfusions. Consider incorporating evaluation of cardiac iron and cardiac function, as well as clinical outcomes, to explore relationship amongst LIC, cardiac iron, serum ferritin and clinical endpoints.

- Recognizing that there may be a subset of patients who may not experience sufficient decreases in body iron burden at highest recommended doses of Exjade®, or who cannot tolerate Exjade®, should such a population emerge, consider conducting a study of some combination of deferoxamine and Exjade.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Alice Kacuba, RN, MSN, RAC, Regulatory Health Project Manager, at (301) 796-1381.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur

11/2/2005 05:14:19 PM

EXJADE®

(deferasirox)

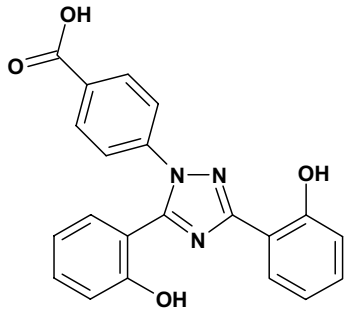
Tablets for Oral Suspension

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/day) was able to induce a mean net iron excretion (0.119, 0.329 and 0.445 mg Fe/kg body weight/d, respectively) within the clinically relevant range (0.1-0.5 mg/kg/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® (deferasirox) 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-catalysed (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, ADVERSE REACTIONS).

Hepatic Insufficiency: Deferasirox is principally excreted by glucuronidation and is minimally (8%) metabolised 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 multi-center, 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 AE. 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/day failed to provide consistent lowering of LIC and serum ferritin levels (Figure 1). Therefore, a starting dose of 20 mg/kg/day is recommended. (See DOSAGE AND ADMINISTRATION).

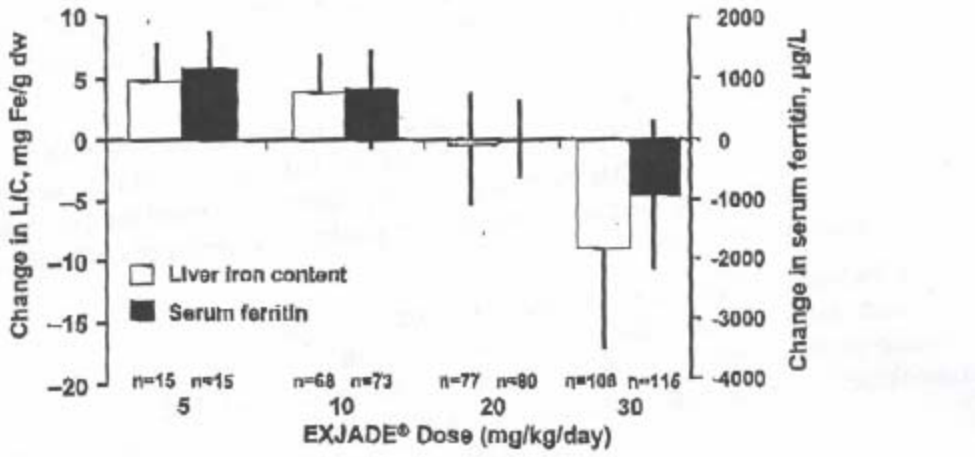


Figure 1. Changes in Liver Iron Concentration and Serum Ferritin Following Exjade (5 to 30 mg/kg per day) in Study 1

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 20-60 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-treated patients experienced dose-dependant 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, four 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 (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 ULN 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 ULN, 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 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 "IA" 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 "IB" 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 "IC" 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

NOVEMBER 2005

Exjade (Deferasirox) Tablets
Company: Novartis Pharmaceuticals Corporation
Application No.: 021882
Approval Date: 11/02/2005

- Medical Review(s)
- Chemistry Review(s)
- Pharmacology Review(s)
- Statistical Review(s)
- Clinical Pharmacology Biopharmaceutics Review(s)
- Administrative Document(s) & Correspondence

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