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) ould 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

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