DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021882/S-015/S-016

ACCELERATED APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Anne Frederick, Ph.D.
Executive Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Frederick:

Please refer to your Supplemental New Drug Application (sNDA) dated December 23, 2011, received December 23, 2011, and your Supplemental New Drug Application (sNDA) dated September 17, 2012, received September 17, 2012 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exjade® (deferasirox) Tablets.

We acknowledge receipt of your amendment(s) dated February 13, March 13, April 18, May 7, May 30, July 13, August 6, August 13, September 25, September 26, October 3 (2), October 9, October 30 (2), November 13, November 19, November 29, November 30, December 5, December 10, December 18, 2012; January 9, January 17, January 21, and January 22, 2013.

The "Prior Approval" supplemental new drug application, S-015, under Accelerated Approval, provides for the addition of a new indication for the use of Exjade® (deferasirox) in the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion dependent thalassemia (NTDT) syndromes and with a liver iron concentration (LIC) of at least 5 milligrams of iron per gram of liver dry weight (mg Fe/g dw) and serum ferritin greater than 300 mcg/L.

The "Prior Approval" supplemental new drug application, S-016, provides for the addition of the adverse event term "worsening anemia" as an adverse drug reaction to Section 6.2 Postmarketing Experience of labeling.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirements (PMRs) specified in your submission dated January 22, 2013. These requirements, along with required completion dates, are listed below.

PMR 1994-1 Conduct a trial to assess the long-term efficacy of Exjade® (deferasirox) in patients with NTDT and high LIC. The trial should assess response rates in the subset of patients with baseline LIC values >15 mg Fe/g dw (proportion of patients achieving an LIC <5 mg Fe/g dw and time to achieving an LIC <5 mg Fe/g dw). Follow-up of all subjects for up to 5 years is necessary.

Final Protocol Submission: 09/2013

Trial Completion:	05/2019
Final Report Submission:	11/2019

PMR 1994-2 Assess the long-term efficacy (and safety) of Exjade® (deferasirox) treatment to a target LIC of 3 mg Fe/g dw followed by one or more treatment holidays until the LIC is ≥5 mg Fe/g dw in patients with NTDT. Follow-up of all subjects for up to 5 years is necessary.

Final Protocol Submission:	09/2013
Trial Completion:	05/2019
Final Report Submission:	11/2019

PMR 1994-3 Conduct a prospective, randomized trial in at least 210 patients with low to intermediate risk myelodysplastic syndromes (MDS) receiving Exjade® (deferasirox) for transfusional iron overload (approximately 140) or placebo (approximately 70) to determine the efficacy and safety of Exjade® (deferasirox) in this population. The trial will continue for 3 years from the date the last patient is enrolled.

Final Protocol Submission:	07/2013
Trial Completion:	03/2018
Final Report Submission:	09/2018

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years because necessary studies are impossible or highly impracticable. This is because the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia (NTDT) with Exjade® (deferasirox) is indicated when the liver iron concentration (LIC) exceeds 5 mg Fe/g dw. Since the annual increase in LIC is less than 0.5 mg Fe/g dw, it is rare for children with NTDT less than 10 years of age to have an LIC which will warrant treatment with Exjade® (deferasirox). Given the rarity of an elevated LIC in this small population that is geographically dispersed, clinical trials would be impossible or highly impractical.

We note that you have fulfilled the pediatric study requirement for ages 10 to 16 years for this application.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Exjade® (deferasirox) was approved on November 2, 2005, we have become aware of serious safety concerns due to the lack of adequate safety information on possible adverse effects of Exjade® (deferasirox) therapy on growth and development of children, the insufficient characterization of the safety profile, including serious safety risks, in adults with Exjade® (deferasirox) therapy of transfusional iron overload states other than those resulting from thalassemia conditions, and the lack of data about the potential for serious safety risks when Exjade® (deferasirox) is used long-term in patients with NTDT as identified from Periodic Safety Update Report (PSUR) submissions. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signals of the serious safety risks of possible adverse effects on growth and development in children, and safe use in adults with iron overload not related to thalassemia.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1994-4 Establish a registry of children (aged 10 to <18 years old at enrollment) with NTDT and treated with Exjade® (deferasirox) for documented iron overload. Study 2422 will follow at least 40 children for up to 5 years to assess and analyze the long-term safety of treatment with Exjade® (deferasirox), including an assessment of growth, compared to children on a regular transfusion program receiving Exjade® (deferasirox) (based on historical data). Provide annual interim reports on enrollment and outcomes.

The timetable you submitted on January 22, 2013 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2013
Interim Report Submission:	12/2014
Interim Report Submission:	12/2015
Interim Report Submission:	12/2016

Interim Report Submission:	12/2017
Interim Report Submission:	12/2018
Interim Report Submission:	12/2019
Interim Report Submission:	12/2020
Study Completion:	06/2021
Final Report Submission:	12/2021

PMR 1994-5 Conduct an enhanced pharmacovigilance study (including proactive surveillance and follow-up of spontaneous reports) to characterize the frequency and severity of adverse Events of Special Interest (ESIs), defined as all deaths and severe or serious events of kidney or liver toxicity, in adults receiving Exjade® (deferasirox) for documented iron overload related to multiple transfusions for myelodysplastic syndrome with anemia requiring transfusions. The specifics regarding targeted safety data collection and analysis, case ascertainment, and processes for meaningful surveillance will be detailed in a protocol to be submitted for FDA review and concurrence prior to study initiation. This study does not replace monitoring and reporting as required by regulations.

The timetable you submitted on January 22, 2013 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2013
Interim Report Submission:	07/2014
Interim Report Submission:	01/2015
Interim Report Submission:	07/2015
Interim Report Submission:	01/2016
Interim Report Submission:	01/2017
Interim Report Submission:	01/2018
Study Completion:	01/2019
Final Report Submission:	07/2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of serious risk of long-term use of Exjade® (deferasirox) in patients with NTDT.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1994-6 Assess the long-term safety of Exjade® (deferasirox) in patients with NTDT by conducting a trial of Exjade® (deferasirox) for the treatment of iron overload (LIC ≥5 mg Fe/g dw) in non-transfusion dependent thalassemia (NTDT) in patients aged 10 years and greater with up to 5 years total follow-up.

The timetable you submitted on January 22, 2013 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	05/2019
Final Report Submission:	11/2019

Submit protocols to your IND 058554, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

PMC 1994-7 Characterize the relationship between LIC and serum ferritin in patients with NTDT at the following times: when a decision on whether to initiate treatment with Exjade® (deferasirox) is being made, and during treatment at times when dose adjustment(s) may be made or when a decision on treatment discontinuation may be made. Perform an analysis of paired LIC and serum ferritin measurements obtained in studies 2209 and 2209E before, during or after treatment with Exjade to determine the positive and negative predictive values of specific thresholds of serum ferritin for LIC values of LIC >5, LIC >7, LIC >15 and LIC <3 mg Fe/g dw.

The timetable you submitted on January 22, 2013 states that you will conduct this study according to the following schedule:

Final Analysis Plan Submission:	07/2013
Analysis Completion:	10/2013
Final Report Submission:	12/2013

Submit clinical protocols to your IND 058554 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

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

If you have any questions, call Mara Miller, Regulatory Project Manager, at (301) 796-0683**.**

Sincerely,

{See appended electronic signature page}

Robert C. Kane, M.D.
Deputy Director for Safety
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

ROBERT C KANE
01/23/2013