CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

206910Orig1s000

Trade Name: JADENU

Generic Name: deferasirox

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: March 30, 2015

Indications: JADENU is indicated for the treatment of chronic iron overload due to blood transfusion (transfusional hemosiderosis) in patients 2 years of age and older and for 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 a serum ferritin greater than 300 mcg/L.

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206910Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	**X**
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	
Microbiology / Virology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPLICATION NUMBER:

206910Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206910

ACCELERATED APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Abbey Abraham, Pharm D.
Senior Associate Director,
Drug Regulatory Affairs
Oncology Global Development
One Health Plaza, Building 337/B10-6
East Hanover, NJ 07936-1080

Dear Dr. Abraham:

Please refer to your New Drug Application (NDA) dated May 30, 2014, received May 30, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jadenu™ (deferasirox) tablets.

We acknowledge receipt of your amendments dated June 4; July 14 and 18; October 2 and 22, 2014; January 22; February 9; March 12, 20, 24, and 27, 2015.

This new drug application provides for the use of Jadenu™ (deferasirox) for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older and for 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 a serum ferritin greater than 300 mcg/L.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

WAIVER OF HIGHLIGHTS SECTION

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). 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 206910**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the products with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 requirement specified in your submission dated February 9, 2015. This requirement, along with required completion dates, is listed below.

PMR 2888-1 Establish a registry for children aged 2 to < 6 years to enroll approximately 200 patients receiving deferasirox and follow them for 5 years. Collect data at least monthly for renal function and blood pressure and yearly for growth and development, and analyze the data for adverse renal reactions and delayed growth and development. Submit your monitoring scheme for our review and comment.

The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/2016

PMR 2888-2 Conduct a trial to assess the long-term efficacy and safety of 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.

The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

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

PMR 2888-3 Conduct a trial to assess the long-term efficacy (and safety) of 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.

The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

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

PMR 2888-4 Conduct a prospective, randomized trial in at least 210 patients with low to intermediate risk myelodysplastic syndromes (MDS) receiving deferasirox for transfusional iron overload (approximately 140 patients) or placebo (approximately 70 patients) to determine the efficacy and safety of deferasirox in this population. The trial will continue for 3 years from the date the last patient is enrolled.

The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

Trial Completion: 03/2018
Final Report Submission: 09/2018

Submit clinical protocols to your IND 058554 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement 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.

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 indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product has orphan designations for these indications, you are exempt from this requirement.

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.

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 signals of serious risks of unintended over chelation that inhibits growth in children, and events of special interest (defined as all deaths and severe or serious events of kidney or liver toxicity); and identify unexpected serious risks of cardiac, hepatic, endocrine and renal toxicities in adults with myelodysplastic syndrome receiving deferasirox for multiple transfusions.

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 2888-5 Conduct a study, using your established registry, to evaluate the risk of growth inhibition in children (aged 10 to <18 years old at enrollment) with NTDT and treated with deferasirox for documented iron overload. Follow at least 40 children for up to 5 years to assess and analyze the long-term safety of treatment with deferasirox, including an assessment of growth, compared to children on a regular transfusion program receiving deferasirox (based on historical data). Provide annual interim reports on enrollment and outcomes.

The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

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 2888-6 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 deferasirox for documented iron overload related to multiple transfusions for myelodysplastic syndrome with anemia requiring transfusions. This study does not replace monitoring and reporting as required by regulations.

The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

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

PMR 2888-7 Complete a study of long-term follow-up (3 years) in 150 patients with myelodysplastic syndromes (MDS) receiving deferasirox to evaluate safety (including cardiac, hepatic, endocrine and renal) and hematologic and clinical benefit of deferasirox in these patients.

The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify the unexpected serious risks of ocular toxicity involving the retina and optic nerve and of long-term exposure to deferasirox in non-transfusion dependent thalassemia.

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

PMR 2888-8 Conduct a trial to assess ocular toxicity in patients receiving deferasirox. 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 deferasirox initiation) and at six month intervals. At least 60 patients should complete 2 years of follow-up.

The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

Final Protocol submission: 10/2015
Final Report Submission: 12/2019

PMR 2888-9 Conduct a trial to assess the long-term safety of deferasirox in patients with NTDT by conducting a trial of 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 March 27, 2015, states that you will conduct this study according to the following schedule:

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

Submit the protocol(s) 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.

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 the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kris Kolibab, Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

ANN T FARRELL
03/30/2015